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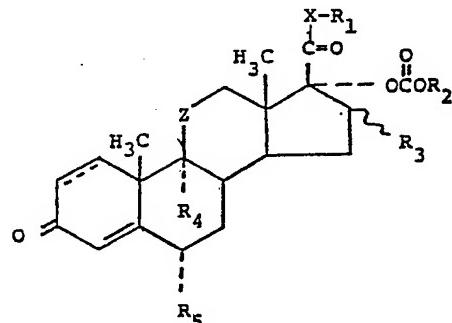
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(54) **Androstene 17 α -carbonate
17 β -carboxylates (and carbo-
thioates)**

(57) Novel anti-inflammatory agents
based on a glucocortico-steroid
structure having a general formula I

defined; X is O or S.

One example is based on the
inactive metabolite cortienic acid
which is activated by the introduc-
tion of non-toxic substituents at po-
sitions 17 α - and 17 β .



the groups R₁ to R₅, and Z being

GB 2079755 A

SPECIFICATION**Soft steroids having anti-inflammatory activity****5 Technical Field of the Invention:**

The invention relates to novel soft steroids having anti-inflammatory activity, pharmaceutical compositions containing said soft steroids, novel chemical intermediates useful in the preparation of the steroids, and processes for preparing said steroids and intermediates.

5

10 Background Art:

Successful predictions on a rational basis of the biological activity of compounds leading to new drugs are the main objective of drug designers. This has usually been achieved by considering a known bio-active molecule as the basis for structural modifications, either by the group or biofunctional moieties approach or by altering the overall physical-chemical properties of the molecule. Thus, the main aim has been to design, synthesize, and test new compounds structurally analogous to the basic bioactive molecule which have, however, improved therapeutic and/or pharmacokinetic properties. Although "vulnerable" moieties have been identified as the ones whose role is the bioactivation or metabolic elimination of the drug after it has performed its role, little or no attention has been paid in the drug-design process to the rational design of the metabolic disposition of the drugs. This has been the case despite the fact that the toxicity of a number of bioactive molecules is due to their increased elimination half-life, stability, or other factors introduced during the design of increasing their activity. Drugs and particularly their metabolic processes contribute to the various toxic processes by formation of active metabolites. The phenomenon of metabolic activation to reactive intermediates which covalently bind to tissue macromolecules is the initial step in cell damage. It is also clear that the most toxic metabolites will not survive long enough to be excreted and identified; thus, studies of the stable metabolites may provide misleading information.

10

It is clear that, in order to prevent and/or reduce toxicity problems related to drugs, the metabolic disposition of the drugs should be considered at an early stage of the drug-design process. This is true particularly when one considers that the body can attack and alter chemically quite stable structures and that, even if a drug is 95% excreted unchanged, the unaccounted small portion can, and most likely will, cause toxicity.

15

"Soft drugs" can be defined as biologically active chemical compounds (drugs) which might structurally resemble known active drugs (soft analogues) or could be entirely new types of structures, but which are all characterized by a predictable *in vivo* destruction (metabolism) to nontoxic moieties, after they achieve their therapeutic role. The metabolic disposition of the soft drugs takes place with a *controllable rate* in a predictable manner.

20

The present inventor has found five major classes of soft drugs. One of the most useful classes was termed the "inactive metabolite" approach which can be advantageously employed to design especially valuable "soft drugs". This approach starts with a known inactive metabolite of a drug or a drug class; followed by modifying the metabolite to resemble structurally (isosteric and/or isoelectronic) the active drug (i.e., activation); and designing the metabolism of the activated species to lead to the starting inactive metabolite after achieving the desired therapeutic role, without the formation of toxic intermediates (i.e., predictable metabolism). The "inactive metabolite" approach further allows controlling the rate of metabolism and pharmacokinetic properties by molecular manipulation in the activation stage. Also, if no useful inactive metabolite is known, one can be designed by the introduction of transporting groups in noncritical structural parts.

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50 Summary of the Invention:

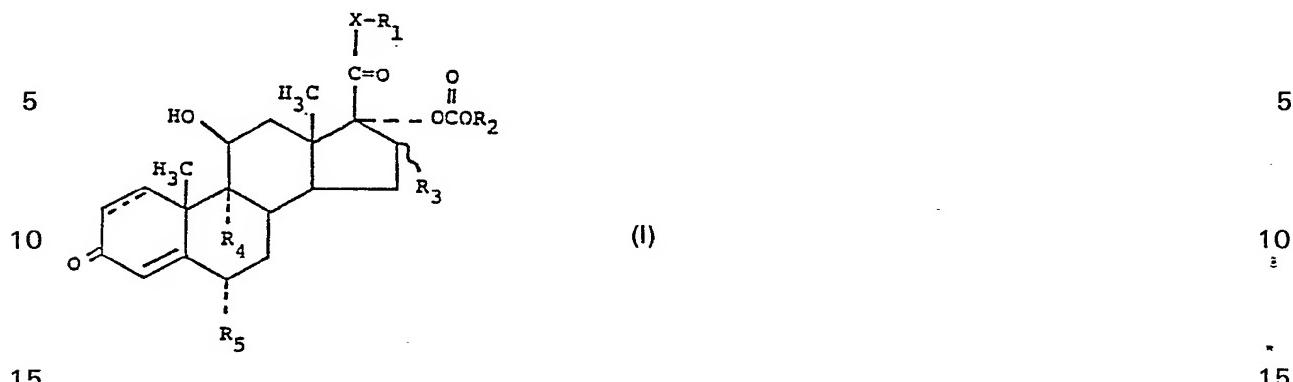
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The present inventor has now applied his inactive metabolite approach to the case of the natural and synthetic glucocorticosteroids and has designed the soft steroidal anti-inflammatory agents of the present invention, beginning with the known inactive natural metabolites of the glucocorticosteroids. Thus, for example, in the case of hydrocortisone, one of its major, inactive metabolites, cortienic acid, i.e., 11 β , 17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylic acid, has been used as a starting point and activated by the introduction of suitable non-toxic 17 α - and 17 β -substituents, which activated derivatives will cleave *in vivo*, after accomplishment of their therapeutic role, to the starting inactive metabolite and other nontoxic moieties.

35

In accord with the foregoing, the present invention provides novel soft steroids having anti-inflammatory activity, said steroids having the structural formula

40



wherein:

R₁ is C₁-C₁₀ alkyl; C₂-C₁₀ (monohydroxy or polyhydroxy)alkyl; C₁-C₁₀ (monohalo or polyhalo)-alkyl; or -CH₂COOR₆ wherein R₆ is unsubstituted or substituted C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl or C₂-C₁₀ alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl.

25 $-\text{NHC}(=\text{O})-(\text{C}_1-\text{C}_{10} \text{ alkyl})$ and $-\text{OC}(=\text{O})-(\text{C}_1-\text{C}_{10} \text{ alkyl})$, or R_6 is 25

unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxy carbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl; or R_1 is $-\text{CH}_2\text{CONR}_7\text{R}_8$ wherein R_7 and R_8 , which can be the same or different, are each hydrogen, lower alkyl, C_3-C_8 cycloalkyl, phenyl or benzyl, or R_7 and R_8 are combined such that $-\text{NR}_7\text{R}_8$ represents the residue of a saturated monocyclic secondary amine; or R_1 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group of phenyl and benzyl substituents defined hereinabove with respect to R_6 ; or R_1 is

40 $\text{R}_2\text{C}(\text{CH}_2-\text{Y}-\text{lower alkyl})$ wherein Y is $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$ or $-\text{O}-$ 40

and R₉ is hydrogen, lower alkyl or phenyl, or R₉ and the lower alkyl group adjacent to Y are combined so that

45 R₁ is a cyclic system of the type -CH- Y wherein Y
 | |
 alkylene

is defined as above and the alkylene group contains 3 to 10 carbon atoms, of which at least 3
50 and no more than 6 50

as hereinabove and R_{10} is hydrogen, lower alkyl, phenyl or haloalkyl;
 R_2 is unsubstituted or substituted C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl or C_2-C_{10}
60 alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower 60

- O
||
alkylsulfinyl, lower alkylsulfonyl, $-\text{NHC}-$ ($\text{C}_1\text{--C}_{10}$ alkyl) 5 5
- O
||
and $-\text{OC}-$ ($\text{C}_1\text{--C}_{10}$ alkyl), or R_2 is unsubstituted or 10 10
- substituted phenyl or benzyl, the substitutents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxy carbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl; 15 15
- R_3 is hydrogen, α -hydroxy, β -hydroxy, α -methyl,
- O
||
 β -methyl, $=\text{CH}_2$, or α - or β - OCOR_2 wherein R_2 is identical 20 20
- to R_2 as defined hereinabove;
- R_4 is hydrogen, fluoro or chloro;
- R_5 is hydrogen, fluoro, chloro or methyl;
- X is $-\text{O}-$ or $-\text{S}-$;
- 25 Z is carbonyl or β -hydroxymethylene;
- and the dotted line in ring A indicates that the 1,2-linkage is saturated or unsaturated.
- A group of preferred compounds of formula (I) consists of those wherein:
- R_1 is $\text{C}_1\text{--C}_6$ alkyl; $\text{C}_1\text{--C}_6$ (monohalo or polyhalo)-alkyl; $-\text{CH}_2\text{COOR}_6$ wherein R_6 is $\text{C}_1\text{--C}_6$ alkyl; 30 30
- $-\text{CH}_2\text{Y}-(\text{C}_1\text{--C}_6$ alkyl) wherein Y is $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$ or $-\text{O}-$; or
- O
||
 $-\text{CH}_2\text{OCR}'_6$ wherein R'_6 is $\text{C}_1\text{--C}_6$ alkyl or phenyl; 35 35
- R_2 is $\text{C}_1\text{--C}_6$ alkyl, $\text{C}_3\text{--C}_8$ cycloalkyl, phenyl, benzyl or $\text{C}_1\text{--C}_6$ (monohalo or polyhalo)alkyl;
- R_3 is hydrogen, α -hydroxy, α -methyl, β -methyl or
- O
||
 α - OCOR_2 40 40
- wherein R_2 is identical to R_2 as defined hereinabove;
- R_4 is hydrogen or fluoro;
- R_5 is hydrogen or fluoro;
- Z is β -hydroxymethylene;
- 45 and X and the dotted line in ring A are defined as hereinabove.
- The invention further provides anti-inflammatory quaternary ammonium salts of selected compounds of formula (I), as discussed in further detail below. Novel intermediates to the compounds of formula (I), e.g., the corresponding compounds wherein R_1 is hydrogen, are 50 50 provided also.
- The soft steroids of formula (I) and quaternary ammonium salts thereof are extremely potent local anti-inflammatory agents; however, by virtue of the fact that their facile *in vivo* destruction leads only to the inactive steroid metabolite, the present compounds have far less systemic activity than the known glucocorticosteroids from whose inactive metabolites they are derived. 55 55
- Indeed, many of the compounds of the present invention are entirely devoid of systemic activity. Such minimal—or non-existent—systemic activity means that the compounds of the present invention can be used in the local (e.g., topical) treatment of inflammatory conditions without the serious systemic side effects which attend use of the known glucocorticosteroids.
- 60 Detailed Description of the Invention and the Preferred Embodiments:** 60
- With respect to the various groups encompassed by the generic terms used here and throughout this specification, the following definitions and explanations are applicable:
- The alkyl, alkenyl and alkylene groupings can be straight or branched-chain groups containing the aforementioned number of carbon atoms. Likewise, the alkyl portions of the alkoxy, 65 65
- alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxy carbonyl, alkanoyloxy, haloalkyl, monoalkylamino,

dialkylamino, monoalkylcarbamoyl, and dialkylcarbamoyl, groupings each can be straight or branched-chain. The term "lower" used in conjunction with any of those groupings or in conjunction with "alkyl" is intended to indicate that each alkyl portion therein can contain 1 to 8 carbon atoms.

- 5 Specific examples of alkyl radicals encompassed by formula (I), whether as specific values for R₁ or R₂, or as a portion of a R₁, R₂, or R₃ group, include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl and their branched-chain isomers, as well as their straight and branched-chain higher homologues in the instances where "alkyl" can contain more than 8 carbon atoms. The alkenyl radicals can be exemplified by vinyl, propenyl and butenyl. Illustrative of the 5
- 10 cycloalkyl and cycloalkenyl radicals are cyclopentyl, cyclohexyl, cyclopentenyl and cyclohexenyl. 10 The alkylene moieties are typified by trimethylene, tetramethylene and the like. The alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxy carbonyl, alkanoyloxy, monoalkylamino, dialkylamino, monoalkylcarbamoyl and dialkylcarbamoyl groupings are of the type

| | | |
|----|--|----|
| 15 | -O-alkyl -S-alkyl -SO-alkyl -SO ₂ -alkyl | 15 |
| 20 | -C=O-alkyl | 20 |
| 25 | -O-C=O-alkyl -NH-alkyl | 25 |
| 30 | alkyl -N alkyl | 30 |
| 35 | -C=O-NH-alkyl | 35 |
| 40 | and alkyl -C-N O alkyl | 40 |
| 45 | | 45 |

respectively, wherein alkyl is as hereinbefore defined and exemplified.

With respect to the structural variables encompassed by the group of preferred compounds of formula (I) identified hereinabove, the term "C₁-C₆ alkyl" is used to refer to a straight or

- 50 branched-chain alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl and the like. In addition, the term "C₁-C₆ (monohalo or polyhalo)alkyl" is used to refer to a straight or branched-chain alkyl group having 1 to 6 carbon atoms substituted with from 1 to 3 halogen atoms, the term "halogen" as used herein including a chlorine atom, a bromine atom, an iodine atom or a 50 fluorine atom. Specific examples of the contemplated monohaloalkyl and polyhaloalkyl groups 55 include chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1-chloroethyl, 2-chloroethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 1,2-dichloroethyl, 1-chloropropyl, 3-chloropropyl, 1-chlorobutyl, 1-chloropentyl, 1-chlorohexyl, 4-chlorobutyl and the like. Also, the term "C₃-C₈ cycloalkyl" is used to refer to a 60 cycloalkyl radical having 3 to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

When R₁ in formula (I) is -CH₂CONR₁R₈ wherein -NR₁R₈ represents the residue of a saturated monocyclic secondary amine, such monocycles preferably have 5 to 7 ring atoms optionally containing another hetero atom (-O-, -S- or -N-) in addition to the indicated nitrogen atom, 65 and optionally bear one or more substituents such as phenyl, benzyl and methyl. Illustrative of 65

residues of saturated monocyclic secondary amines which are encompassed by the $-NR_7R_8$ term are morpholino, 1-pyrrolidinyl, 4-benzyl-1-piperazinyl, perhydro-1,2,4-oxathiazin-4-yl, 1- or 4-piperazinyl, 4-methyl-1-piperazinyl, piperidino, hexamethyleneimino, 4-phenylpiperidino, 2-methyl-1-pyrazolidinyl, 1- or 2-pyrazolidinyl, 3-methyl-1-imidazolidinyl, 1- or 3-imidazolidinyl, 4-

5 benzylpiperidino and 4-phenyl-1-piperazinyl.

Selected compounds of formula (I), i.e. compounds wherein R_1 is α -haloalkyl, readily form the corresponding soft quaternary ammonium salts which are likewise useful as soft anti-inflammatory agents. Thus, for example, the selected haloalkyl derivative of formula (I) can simply be reacted with a tertiary amine ($\geq N$) or an unsaturated amine ($\geq N$) to afford the corresponding

10 quaternary ammonium salt. The reactants are generally used in approximately equimolecular proportions and the reaction is conducted in the presence of an inert solvent (e.g., ether, acetonitrile, CH_2Cl_2 or the like), at a temperature of from room temperature to the reflux

15 temperature of the solvent, for approximately 2 to 24 hours. Alternatively, the reaction can be conducted in the absence of a solvent by mixing the two reactants together and maintaining

15 them at room temperature or between 20° to 70°C for 2 to 24 hours. In either case, the crystalline salt formed can be purified by crystallization from an ether-ethanol mixture, or the like.

The expression "unsaturated amine" used above denotes N-heterocyclic unsaturated systems having 3 to 10 members in the ring, and substituted derivatives thereof, where the unsaturation 20 corresponds to the maximum number of non-cumulative double bonds, provided that the nitrogen atom contains no hydrogen atom as a substituent. The following examples will sufficiently illustrate the scope of the defined term:



| | | | | |
|----|------------------------|--|--|----|
| | Pyrazine | | | |
| 5 | Pyrimidine | | | 5 |
| 10 | Pyridazine | | | 10 |
| 15 | 2-Methylisoindole | | | 15 |
| 20 | 3H-indole | | | 20 |
| 25 | Isoquinoline | | | 25 |
| 30 | Phthalazine | | | 30 |
| 35 | Quinoxaline | | | 35 |
| 40 | Quinazoline | | | 40 |
| 45 | Phenazine | | | 45 |
| 50 | Iothiazole | | | 50 |
| 55 | 10-Methylphenothiazine | | | 55 |

- Substituted derivatives of the unsaturated amines include groups as shown above containing one or more alkyl, $-COO(alkyl)$ or $-OCO(alkyl)$ substituents.
- With respect to the expression "tertiary amine", this expression denotes amines wherein the nitrogen atom has no hydrogen atoms attached thereto and which are not among the N-heterocyclic unsaturated systems encompassed by the expression "unsaturated amine" as defined above. Typically, the term "tertiary amine" includes trialkylamines, wherein the alkyl groups, which can be the same or different, each preferably contain 1 to 8 carbon atoms; trialkoxyamines wherein the alkoxy portions each contain 1 to 8 carbon atoms; tertiary saturated

cyclic amines such as quinuclidine or substituted quinuclidine (e.g., 3-acetoxyquinuclidine); and N-substituted derivatives of secondary saturated cyclic amines [e.g., an N-substituted derivative of morpholine, pyrrolidine, imidazolidine, pyrazolidine, piperidine or piperazine, wherein the N-substituent can be a group such as (C₁-C₆)alkyl], optionally containing additional substituents

5 such as methyl.

5

Preferred quaternary ammonium salts include those derived from 1,2-dimethylpyrrolidine, 3-acetoxyquinuclidine, 1-methylpyrrolidine, triethylamine and N-methylimidazole. Especially preferred are the quaternary ammonium salts derived from the reaction of the aforesaid amines with compounds of formula (I) wherein Z is β -hydroxymethylene and R₁ is chloromethyl, most

10 especially when R₂ is lower alkyl.

10

While all of the compounds encompassed by formula (I) above essentially satisfy the objectives of the present invention, nevertheless certain groups of compounds remain preferred. A "first" group of preferred compounds of formula (I) has been set forth in the *Summary of the Invention* hereinabove.

15

15 Another preferred group of compounds consists of the compounds of formula (I) wherein Z, X, R₁ and R₂ are defined as hereinabove, and the remainder of the structural variations are identical to those of hydrocortisone (i.e., R₃, R₄ and R₅ are each a hydrogen atom and the 1,2-linkage is saturated) or of prednisolone (i.e., R₃, R₄ and R₅ are each a hydrogen atom and the 1,2-linkage is unsaturated), most especially when R₁ and R₂ are as defined with respect to the "first" group

20

20 of preferred compounds set forth hereinabove.

20

Another preferred group of compounds consists of the 6 α - and/or 9 α -fluoro and 16 α - or 16 β -methyl congeners of the compounds indicated in the preceding paragraph. Within this group, the compounds wherein Z, X, R₁ and R₂ are defined as hereinabove and the remaining structural variables are identical to those of fludrocortisone, betamethasone and dexamethasone are

25

25 particularly preferred, most especially when R₁ and R₂ are as defined with respect to the "first" group of preferred compounds set forth hereinabove. Other compounds of particular interest within this group are those wherein Z, X, R₁ and R₂ are defined as hereinabove and the remaining structural variables are identical to those of triamcinolone, flumethasone, fluprednisolone or paramethasone, particularly when R₁ and R₂ are as defined with respect to the "first"

30

30 group of preferred compounds set forth hereinabove. Yet other interesting compounds are those wherein Z, X, R₁ and R₂ are defined as hereinabove, R₃ is



35 α -OCOR₂, and the remaining structural variables are identical

35

to those of triamcinolone, particularly when R₁ and R₂ are as defined with respect to the "first" group of preferred compounds set forth hereinabove.

40

In each of the groups of compounds indicated in the three preceding paragraphs, the 40 compounds wherein X is oxygen are particularly preferred. Most especially preferred are the compounds encompassed by the groups indicated above wherein Z is β -hydroxymethylene, wherein X is oxygen, wherein R₂ is C₁-C₆ alkyl (particularly methyl, ethyl, propyl or isopropyl), and wherein R₁ is C₁-C₆ alkyl, C₁-C₆ (monohalo)alkyl (particularly chloromethyl) or -CH₂-Y-(C₁-C₆ alkyl) wherein Y is defined as hereinabove (particularly when the C₁-C₆ alkyl group is 45 methyl).

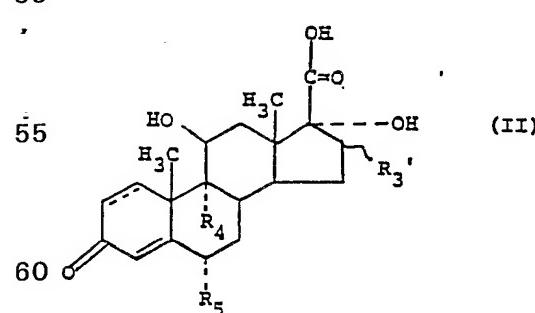
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The compounds of formula (I) can generally be prepared by known methods, the method of choice being dependent on the identity of the various substituents in the desired final product.

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One generally useful method for the preparation of the compounds of formula (I) wherein Z is β -hydroxymethylene and X is oxygen utilizes steroidal starting materials of the formula

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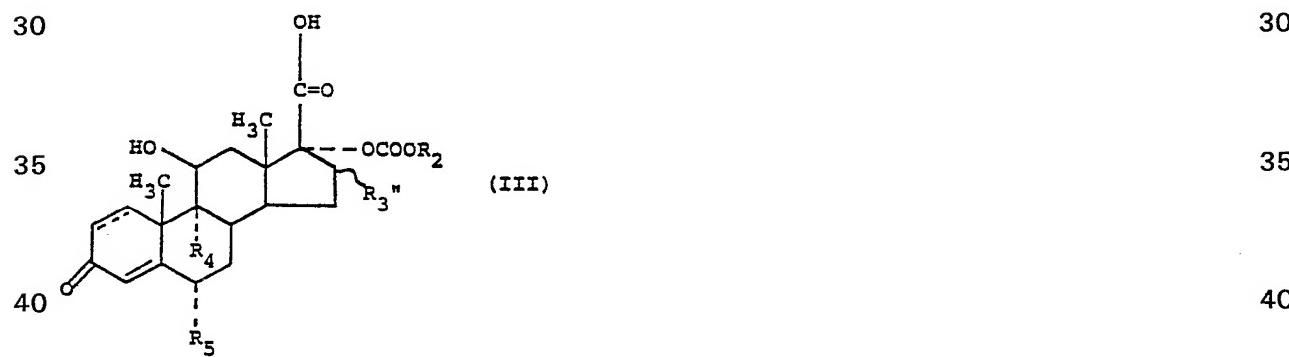
65 wherein R₄, R₅ and the dotted line in ring A are defined as before and R_{3'} is hydrogen, α -

65

methyl, β -methyl, α -OH, β -OH or $=\text{CH}_2$ (and which can be conveniently prepared by treatment of the corresponding 21-hydroxypregnolones of the formula



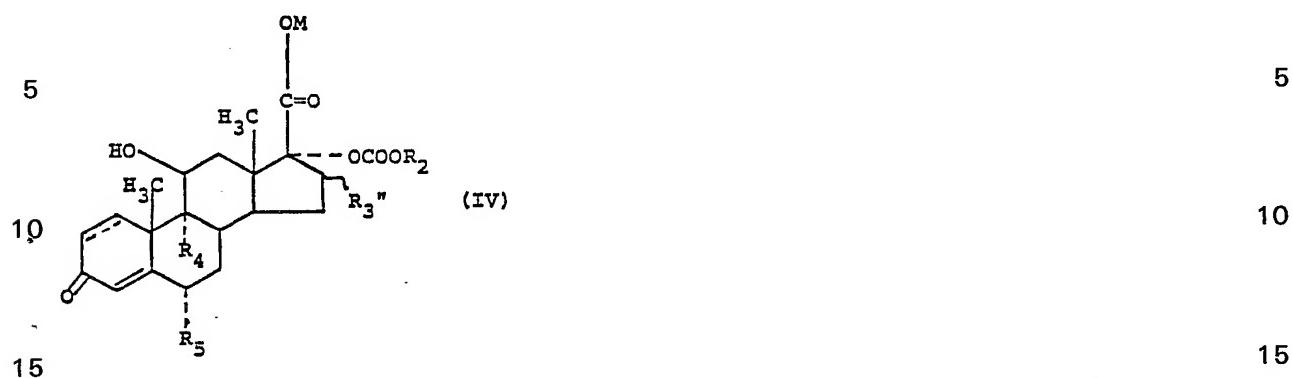
wherein R_4 , R_5 , R_3' and the dotted line in ring A are defined as above with NaIO_4 in a suitable organic solvent at room or elevated temperature.) According to this process of the invention, a starting material of formula (II) is reacted with $R_2\text{OCOCl}$ or $R_2\text{OCOBr}$ (formed by reacting $R_2\text{OH}$ with COCl_2 or COBr_2 , wherein R_2 is defined as above), under anhydrous conditions, in an appropriate inert organic solvent such as dichloromethane, chloroform or tetrahydrofuran, preferably in the presence of a suitable acid acceptor (e.g., triethylamine, pyridine, calcium carbonate or other appropriate base). Time and temperature are not critical factors; however, the reaction is conveniently carried out at a temperature between 0°C and room temperature, for about 1 to 6 hours. The resultant novel 17β -carboxylic acid 17α -carbonate has the formula



wherein R_2 , R_4 , R_5 and the dotted line in the A ring are defined as above and R_3'' is H, α - CH_3 , β - CH_3 , α - OCOOR_2 , β - OCOOR_2 or $=\text{CH}_2$. When R_3' in the starting material of formula (II) is α -OH or β -OH, sufficient $R_2\text{OCOCl}$ or $R_2\text{OCOBr}$ is generally employed to ensure formation of the carbonate grouping at the 16-position as well as at the 17-position [i.e., when R_3' in formula (II) is OH, R_3'' in the resultant intermediate of formula (III) is α - or β - OCOOR_2].

Sometimes, when a compound of formula (I) wherein R_2 contains a sulfinyl or sulfonyl grouping is desired, such a grouping is not introduced via the $R_2\text{OCOCl}/R_2\text{OCOBr}$ reaction, but is prepared from the corresponding thio-containing R_2 derivative at a later stage in the synthetic scheme, as will be discussed in more detail below.

After the above-described introduction of the 17α -substituent, the resultant novel intermediate of formula (III) is converted to its corresponding metal salt of the formula



wherein R_2 , R_3'' , R_4 , R_5 and the dotted line in the ring A are defined as above, and M is a suitable metal, e.g. alkali metal (such as sodium or potassium), alkaline earth metal/2, or thallium or NH_4^+ . The novel salt of formula (IV) is typically formed by reacting the steroid of formula (III) with a hydroxide (MOH) or alkoxide (MOR) in an appropriate organic solvent, such as ethyl ether or tetrahydrofuran, at a temperature of 0°C to room temperature, for 0.5 to 4 hours. Then, the salt of formula (IV) is reacted with a compound of the formula R_1-W wherein R_1 is defined as hereinabove and W is halogen, to afford the desired final product of formula (I). This step of the reaction sequence can be conveniently conducted at room temperature for about 1 to 24 hours, or at the boiling of the solvent (i.e. acetonitrile, THF, etc.) When it is desired to introduce a halo-substituted R_1 grouping into the steroid, e.g., when a compound of formula (I) wherein R_1 is chloromethyl is desired, it has been found that the reaction proceeds well using hexamethylphosphoramide as the solvent at lower temperatures (0–10°C) and employing a R_1-W reactant wherein W is iodine (e.g., iodochloromethane). When a non-halogen containing R_1 grouping is desired (e.g., $R_1 =$ alkyl or $-CH_2COOR_6$ where R_6 is alkyl, etc.), no such restrictions need be placed on the R_1-W reactant or on the solvent; thus, W can be any halogen, preferably chloro or bromo, and the usual organic solvents such as dimethylformamide, dichloromethane, acetonitrile, tetrahydrofuran or chloroform can, if desired, be used instead of hexamethylphosphoramide. When a compound of formula (I) wherein R_1 contains a sulfinyl or sulfonyl grouping is desired, such a grouping is not generally introduced via the R_1-W reaction, but is subsequently prepared from the corresponding thio steroid, as described below.

The compounds of formula (I) wherein R_1 (or R_2) is a sulfinyl- or sulfonyl-containing grouping can be prepared by oxidation of the corresponding thio steroids. Thus, for example, a compound of formula (I)

40 wherein R_1 is $-CH-S-$ (lower alkyl) [wherein R_9 is H,



45 lower alkyl, or combined with the lower alkyl group adjacent to S to form a cyclic system, as described hereinabove] can be reacted with 1 equivalent of *m*-chloroperoxybenzoic acid at 0–25°C for 1 to 24 hours, in a suitable solvent such as chloroform, to afford the corresponding compound of formula (I) wherein R_1 is

50 $-CH-S-$ (lower alkyl), or with 2 equivalents of



55 *m*-chloroperoxybenzoic acid to afford the corresponding

55 compound of formula (I) wherein R_1 is $-CH-SO_2-$ (lower alkyl).



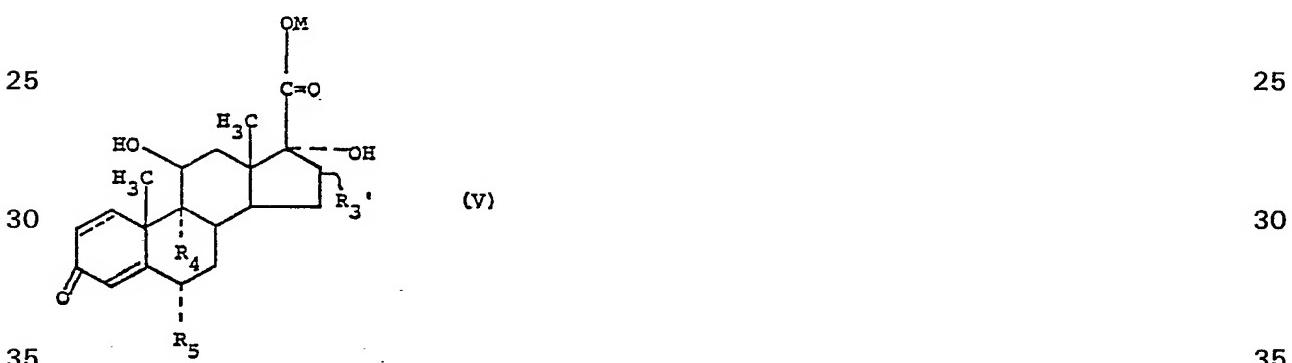
60 This type of reaction can also be utilised to prepare compounds of formula (I) wherein R_1 is $-CH_2COOR_6$ wherein R_6 is substituted alkyl, cycloalkyl, cycloalkenyl, alkenyl, phenyl, or benzyl, wherein the substituent is lower alkylsulfinyl or lower alkylsulfonyl, from the corresponding lower alkylthio-substituted formula (I) steroids; to prepare compounds of formula (I) wherein R_1 is lower alkylsulfinyl- or alkylsulfonyl-substituted phenyl or benzyl from the corresponding lower

65 alkylthio-substituted formula (I) steroids; and to prepare compounds of formula (I) wherein R_2 is

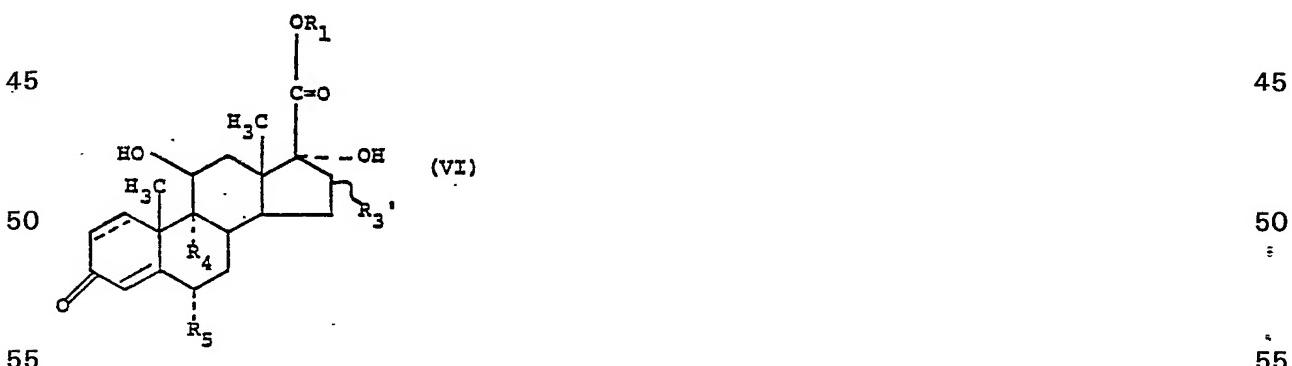
substituted alkyl, cycloalkyl, cycloalkenyl, alkenyl, phenyl or benzyl wherein the substituent is lower alkylsulfinyl or lower alkylsulfonyl, from the corresponding lower alkylthio-substituted formula (I) steroids.

- When the compounds of formula (I) wherein R_3 is α - or β -hydroxy are desired, same can be
 5 prepared by partial acid hydrolysis of the corresponding compounds of formula (I) wherein R_3 is α - or β -OCOOR₂, in a suitable solvent medium. Use of a mild reagent, e.g., oxalic acid in
 methanol, is desirable. Alternatively, hydrolysis of the 16-carbonate to the 16-hydroxy com-
 pound could be carried out at an earlier stage in any synthetic scheme described herein after the
 introduction of the 16,17-carbonate groupings, e.g., selective hydrolysis of an intermediate of
 10 formula (III) having 16 and 17 carbonate groupings to the corresponding 16-hydroxy 17-
 carbonate, followed by conversion to the corresponding compound of formula (I) as described
supra.
 10

- Another process for the preparation of the compounds of formula (I) wherein Z is β -
 hydroxymethylene and X is oxygen utilizes the same 17 α -hydroxy-17 β -carboxylic acid starting
 15 materials of formula (II) as are employed in the synthetic scheme described *supra*, but involves
 formation of the 17 β -COOR₁ grouping prior to, rather than after, introduction of the 17 α -
 OCOOR₂ substituent. Essentially, the same non-steroidal reactants, reaction conditions, etc., as
 described above are used for the introduction of each group. Thus, the starting material of
 20 formula (II) is first reacted with MOH or MOR to form the corresponding intermediate of the
 formula
 20



- wherein R_3' , R_4 , R_5 and M and the dotted line in ring A are defined as above, which is then
 reacted with R_1W wherein R_1 and W are defined as above, to afford the corresponding 17 β -
 40 carboxylate of the formula
 40



- wherein R_1 , R_3' , R_4 , R_5 and the dotted line in ring A are defined as above, which is in turn
 reacted with R_2OCOCl or R_2OCOBr wherein R_2 is defined as above, to afford the corresponding
 60 17 α -carbonate of formula (I). The various parameters of the process of converting (II) to (V) are
 the same as those discussed in detail above with respect to the conversion of (III) to (IV).
 Likewise, the process parameters for converting (V) to (VI) parallel those detailed above with
 respect to converting (IV) to (I). Similarly, the process parameters for converting (VI) to (I) are
 basically the same as those given above for the conversion of (II) to (III). Thus, again, when the
 65 starting material contains a 16-hydroxy group, the 16, 17-dicarbonate of formula (I) will be
 65

formed which can then be selectively hydrolyzed, if desired, to the corresponding 16-hydroxy-17-carbonate of formula (I). And, again, the compounds of formula (I) in which R₁ or R₂ is a sulfinyl- or sulfonyl-containing grouping can be conveniently prepared by oxidation of the corresponding thio-containing compounds of formula (I) as detailed hereinabove. Alternatively,

5 the compounds of formula (I) wherein R₁ is a sulfinyl-

5

or sulfonyl-containing group [e.g., when R₁ is -CH-SO-

|
R₉

10

10

(lower alkyl) or -CH-SO₂- (lower alkyl)] can be prepared

|
R₉

15

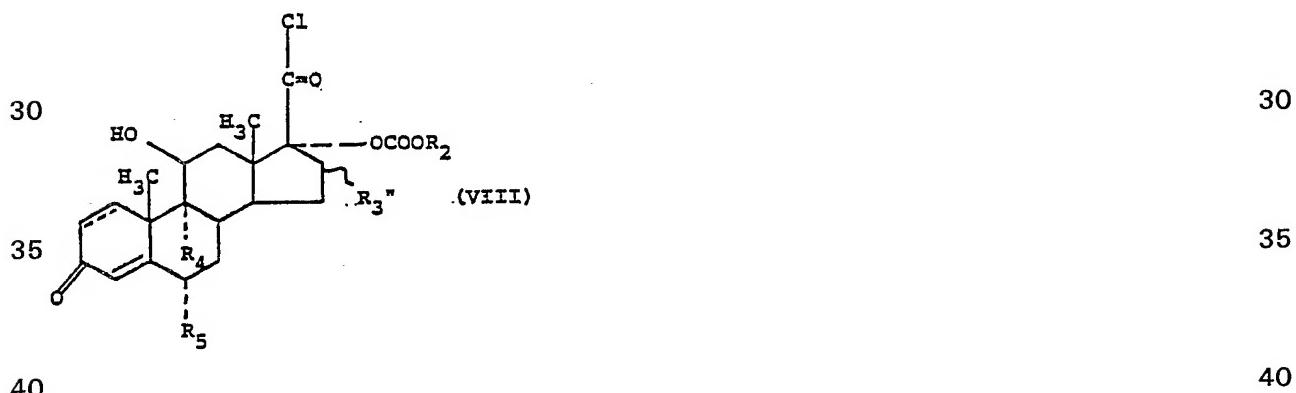
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by oxidation, preferably with *m*-chloroperoxybenzoic acid, of the corresponding compounds of formula (VI) in which R₁ is a thio-containing group, followed by introduction of the 17 α -OCOOR₂ substituent to the resultant sulfinyl or sulfonyl compound.

Another possible process for the preparation of the compounds of the present invention, 20 which can be used to prepare compounds of formula (I) wherein Z is β -hydroxymethylene and X is oxygen or sulfur, utilizes the 17 β -carboxylic acid 17 α -carbonate intermediates of formula (III) above. According to this process, an intermediate of formula (III) is successively treated, first with a mild acyl chloride forming agent, e.g. such as diethylchlorophosphate or oxalyl chloride, to form the corresponding novel acid chloride of the formula

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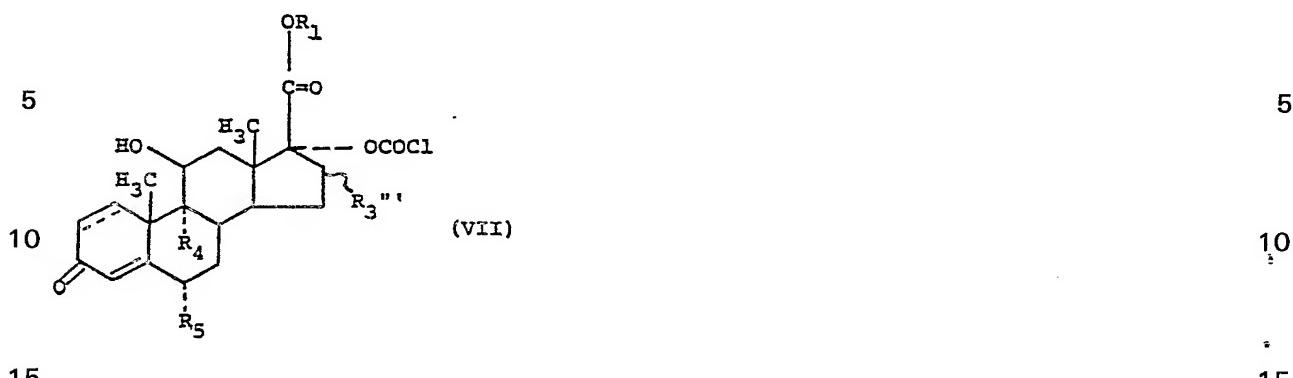
wherein R₂, R_{3''}, R₄, R₅ and the dotted line in ring A are defined as above, and then with R₁XM' wherein R₁ and X are defined as before, and M' is hydrogen or M (M is defined as above), in an insert solvent (e.g., CHCl₃, THF, acetonitrile or DMF), at a temperature between about 0°C and 45 the boiling point of the solvent, for 1 to 6 hours, to afford the corresponding compound of formula (I). When using a compound of the formula R₁XM' wherein M' is hydrogen, an acid scavenger such as triethylamine is preferably present in the reaction system. The two steps of this process can be very conveniently run in the same solvent, without isolating the acid chloride of formula (VIII) formed in the first step. This process is of particular value when a compound of 50 formula (I) wherein X is S is desired.

45

Yet another desirable process for the preparation of the compounds of formula (I) wherein Z is β -hydroxymethylene and X is oxygen utilizes the 17 α -hydroxy-17 β -carboxylates of formula (VI) above. According to this process, an intermediate of formula (VI) is reacted with phosgene, in a suitable organic solvent (e.g., toluene, benzene, CH₂Cl₂ or acetonitrile) at a low temperature 55 (-20°C to room temperature, e.g., 0°C), for about 2 hours (or until the reaction is complete). Evaporation to remove solvent and excess phosgene affords the desired novel 17 α -chlorocarbo-nyloxy-17 β -carboxylate intermediate of the formula

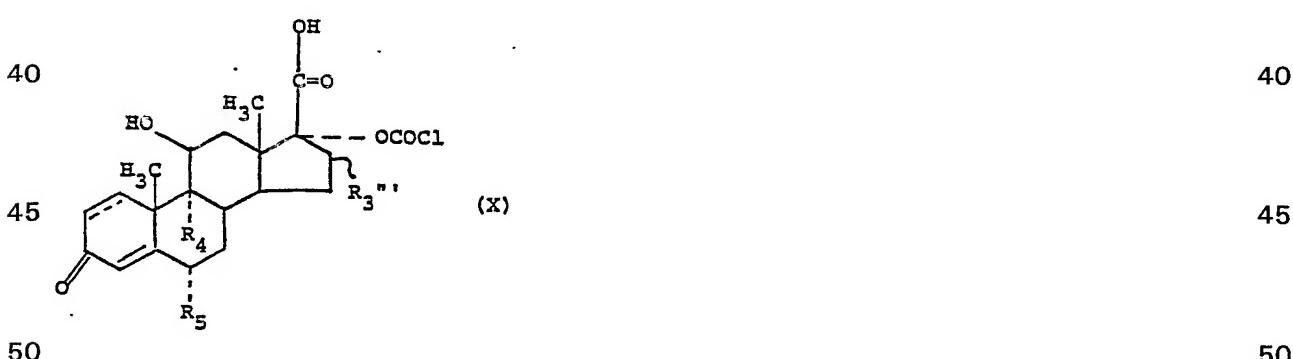
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wherein R_1 , R_4 , R_5 and the dotted line in ring A are defined as above, R_3''' is hydrogen, α -methyl, β -methyl, α -OCOCl, β -OCOCl or =CH₂. When R_3' in the starting material of formula (VI) is hydroxy, sufficient phosgene is generally employed to ensure formation of the chlorocarbonyloxy grouping at the 16-position as well as the 17-position [i.e., when R_3' in formula (VI) is α -OH or β -OH, R_3''' in the resultant intermediate of formula (VII) is α - or β -OCOCl]. The intermediate of formula (VII) is then reacted with a compound of the formula R_2OM' wherein R_2 and M' are defined as above, in an inert solvent, preferably in the presence of an acid scavenger (e.g. triethylamine), to afford the corresponding compound of formula (I). When R_2OM' is an alcohol of the formula R_2OH , the reaction is conducted under the same conditions as in the reaction for conversion of compound (II) to compound (III). On the other hand, if a compound of the formula R_2OM is employed as R_2OM' , the reaction conditions are described as above for conversion of compound (VIII) to compound (I). When R_3''' in the formula (VII) is OCOCl, sufficient R_2OM' is generally utilized to ensure conversion of both the 16- and 17 α -substituents to OCOOR₂ groupings in the final product. And, again, the 16-hydroxy and the sulfinyl- and sulfonyl-containing compounds of formula (I) are most conveniently formed as a final step in the synthesis.

As a variation of the process described immediately above, a steroid 17 α -hydroxy-17 β -carboxylic acid starting material of formula (II) can be reacted with phosgene as described above, to afford the 17 α -chlorocarbonyloxy-17 β -carboxylic acid intermediate of the formula



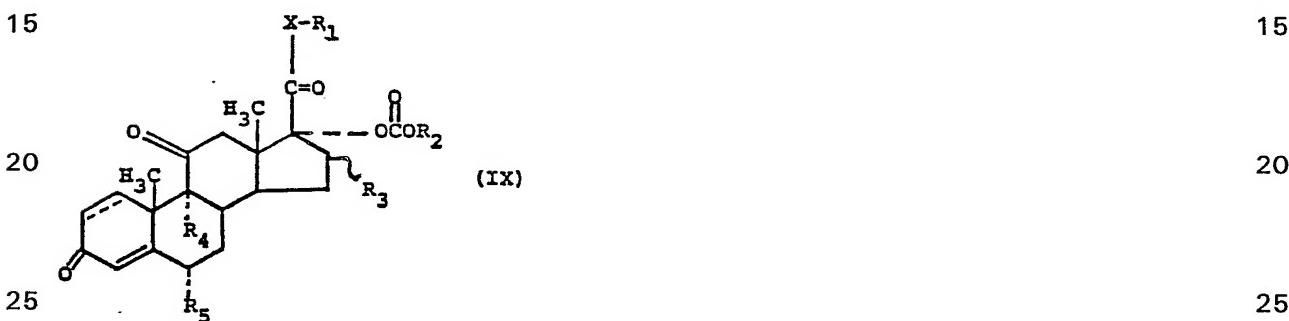
wherein R_3''' , R_4 , R_5 and the dotted line in ring A are defined as above, which can then be reacted with R_2OM' as described *supra*, to afford the corresponding compound of formula (III) above. The novel intermediate can then be converted to a corresponding compound of formula (I) as described *supra*. Once again, the 16-hydroxy and the sulfinyl and sulfonyl derivatives are best prepared as a final step.

Still another process for the preparation of the compounds of formula (I) wherein Z is β -hydroxymethylene and X is oxygen utilizes the 17α -hydroxy- 17β -carboxylates of formula (VI) above. In accord with this method, an intermediate of formula (VI) is reacted with an excess

amount of a carbonate of the formula R_2OCOR_2 (which can be
conveniently prepared by reacting phosgene with 2 equivalents of R_2OH) in the presence of an

include tertiary alkyl amines such as triethylamine, trimethylamine or the like; aromatic amines such as pyridine, 4,4-dimethylamino-pyridine, quinoline or the like; secondary alkyl amines such as diethylamine, dimethylamine or the like; and inorganic bases such as sodium hydroxide, potassium hydroxide, potassium bicarbonate, or the like. Preferably, pyridine and potassium bicarbonate are employed. Examples of suitable inert solvents for use in the hydrolysis include water; lower alcohols such as ethanol, methanol or the like; ethers such as dimethyl ether, diethyl ether, dimethoxyethane, dioxane, tetrahydrofuran, or the like; halogenated hydrocarbons such as dichloromethane, chloroform or the like; tertiary amines such as pyridine, triethylamine or the like; or a mixture of two or more of the solvents mentioned above. The reaction is usually carried out at a temperature of from about 0 to 100°C, preferably at room temperature to 50°C, for 1 to 48 hours, preferably for 2 to 5 hours.

In yet another aspect, the present invention provides novel compounds of the formula



wherein R₁, R₂, R₃, R₄, R₅, X and the dotted line in ring A are as defined with respect to formula (I) above. The 11-keto compounds of formula (IX) can be prepared by the procedures described hereinabove for the preparation of the corresponding 11β-hydroxy compounds of formula (I). Thus, a starting material corresponding to formula (II) but having an 11-keto group is reacted with R₂OCOCl or R₂OOCBr, to afford the corresponding novel intermediate corresponding to formula (III) but having an 11-keto group; that intermediate is then converted to its metal salt, which corresponds to formula (IV) except for the presence of an 11-keto instead of an 11β-hydroxy group; and the metal salt is then reacted with R₁W to afford the corresponding compound of formula (IX). All reaction conditions are as previously described with respect to the corresponding processes for preparing the corresponding compounds of formula (I). Also, the preparation of the compounds of formula (IX) wherein R₁ is a sulfinyl- or sulfonyl-containing grouping or wherein R₃ is hydroxy generally proceeds as a final step in the synthetic scheme in a manner analogous to that used for the corresponding compounds of formula (I). Further, all of the above described alternative processes for the preparation of the compounds of formula (I) are equally applicable to the preparation of the compounds of formula (IX) by simply substituting the 11-oxo starting material for the corresponding 11β-hydroxy steroids used therein, e.g., replacing the 11-hydroxy group in formulas (V), (VI), (VII), (VIII), (X) and (XI) with an 11-oxo group and otherwise proceeding as described hereinabove for the reactions (II)→(V)→(VI)→(I); (III)→(VIII)→(I); (VI)→(VII)→(I); (II)→(X)→(I); (VI)→(I), etc.

Also, the compounds of formula (IX) can be prepared by reacting the corresponding compounds of formula (I) with an oxidizing agent. The oxidation of a compound of formula (I) in order to convert it into the corresponding compound of formula (IX) is usually carried out by using an oxidizing agent in an appropriate solvent. The solvent may be any conventional solvent, for example, water, an organic acid (e.g. formic acid, acetic acid, trifluoroacetic acid), an alcohol (e.g. methanol, ethanol), a halogenated hydrocarbon (e.g. chloroform, dichloromethane), or the like. The oxidizing agent may also be any conventional agent which is effective for oxidizing a hydroxy group to a carbonyl group, for example, pyridinium chlorochromate, chromium trioxide in pyridine, hydrogen peroxide, dichromic acid, dichromates (e.g. sodium dichromate, potassium dichromate), permanganic acid, permanganates (e.g. sodium permanganate, potassium permanganate) or the like. The oxidizing agent is usually used in an amount of 1 mole or more, preferably 1 to 3 mole, per mole of the compound of formula (I). The reaction is usually carried out at a temperature of 0 to 40°C, preferably at around room temperature, for about 6 to 30 hours.

The novel compounds of formula (IX) are useful as soft steroidal anti-inflammatory agents and also *in vivo* or *in vitro* precursors of the corresponding 11β-hydroxy compounds. Thus, the compounds of formula (IX) can be reduced *in vitro* to afford the corresponding compounds of formula (I), using a reducing agent known to be capable of reducing the 11-oxo group to an a

11 β -hydroxy group without modifying the remainder of the steroidal starting material. Typically, microbiological reduction is advantageous for carrying out the desired conversion, although chemical reduction also is possible. Further, the compounds of formula (IX) may be formulated into appropriate dosage forms (e.g., retention enemas) for the treatment of conditions such as 5 ulcerative colitis. In such dosage forms, it is thought that the compounds of formula (IX) are 5 microbiologically reduced by bacteria in the body (e.g. in the colon) to the highly active 11 β -hydroxy steroids, which elicit the desired anti-inflammatory response.

The preferred compounds of formula (IX) are those which are precursors of the preferred compounds of formula (I) wherein Z is β -hydroxymethylene, namely corresponding 11-keto 10 compounds of formula (IX). An especially preferred group of compounds of formula (IX) consists 10 of those wherein X, R₁ and R₂ are defined as above with respect to formula (I) and the remaining structural variations are identical to those of cortisone (i.e. R₃, R₄ and R₅ are each a hydrogen atom and the 1,2-linkage is saturated), of prednisone (i.e. R₃, R₄ and R₅ are each 15 hydrogen and the 1,2-linkage is unsaturated), or of the 6 α - and/or 9 α -fluoro and the 16 α - or 15 16 β -methyl congeners thereof, particularly when R₁ and R₂ are as defined with respect to the "first" group of preferred compounds set forth hereinabove. Most especially preferred of these derivatives are those wherein X is oxygen, R₂ is C₁-C₆ alkyl and R₁ is C₁-C₆ alkyl, C₁-C₆ (monohalo)alkyl [particularly chloromethyl] or -CH₂-Y-(C₁-C₆ alkyl) [particularly -CH₂-Y-CH₃].

The results of various activity studies of representative species of the invention, discussed in 20 detail below, clearly indicate the potent anti-inflammatory activity and the minimal systemic activity/toxicity of the soft steroids of formula (I). In view of this desirable separation of local and systemic activities, the compounds of the invention can be used in the treatment of topical or other localized inflammatory conditions without causing the serious systemic side effects typically exhibited by the known natural and synthetic glucocorticosteroids such as cortisone, 25 hydrocortisone, hydrocortisone 17 α -butyrate, betamethasone 17-valerate, triamcinolone, betamethasone dipropionate and the like.

THYMUS INVOLUTION TEST

The test animals were female Sprague/Dawley rats weighing approximately 40-45 grams 30 each. One side of each ear of each rat was treated with a total of 25 microliters of a solution (ethanol/isopropyl myristate or acetone/isopropyl myristate, 90/10) containing the amount of 30 test compound indicated below. Animals which were treated identically, save for omission of the test compound, served as controls. After 24 hours, all rats were sacrificed and weighed, and their thymi were removed and weighed. The results are tabulated in Table I below, the weights 35 of the thymi being expressed as mg/100 g of rat.

TABLE I
Effect of topically administered soft steroids and reference steroids on thymus weight in rats.

| Test Compound | Amount of Test Compound Applied (μmol) | Number of Rats | Total Weight per Rat (g) | | Starting Final | Gain $\pm \text{SD}$ |
|---|---|----------------|--------------------------|-----------------|----------------|----------------------|
| | | | mg Thymus | $\pm \text{SD}$ | | |
| None (Control) | -- | 8 | 36.4 \pm 2.9 | | 48.44 | 61.42 |
| Hydrocortisone | 0.75 | 8 | 27.4 \pm 4.5 | | 49.44 | 61.15 |
| Chloromethyl 11 β -hydroxy-17 α - methoxycarbonyl- oxyandrost-4-en- 3-one-17 β -carboxy- late | 0.75 | 8 | 34.7 \pm 3.1 | | 48.06 | 62.10 |
| Chloromethyl 17 α -ethoxycar- bonyloxy-11 β - hydroxyandrost- 4-en-3-one-17 β - carboxylate | 0.75 | 7 | 30.9 \pm 2.4 | | 45.57 | 60.60 |
| | | | | | | 33 \pm 6 |

The change in weight in the thymi is a measure of systemic activity and hence of toxicity. The lower the weight of the thymi, the greater the systemic activity. As can be seen from the above data, even hydrocortisone, the natural glucocorticoid, causes a significant decrease in thymus weight compared to the control. The decreases caused by equal doses of representative species 5 of the invention are much less significant, indicating those compounds have much less systemic activity than hydrocortisone. 5

BLANCHING STUDIES

McKenzie-type human blanching studies were undertaken to study the blanching effects of a 10 representative test compound of the invention, chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate. The ability of a compound to cause blanching in humans has been found to correlate closely with its anti-inflammatory activity. 10

The test compound was dissolved in ethanol/isopropyl myristate (90/10 or 70/30) at 0.03, 0.01, 0.003, 0.001 and 0.0003 M concentrations. 50 Microliter aliquots of each solution were 15 applied to separate gauze portions of a bandage of the type commonly used for allergy testing and the bandage was applied to the forearm. After 6 hours of occlusion, the bandage was removed. After 1 to 5 hours after removal of the bandage, blanching was observed even at the lowest concentrations of test compound. 15

When hydrocortisone was tested according to the above procedure comparing it directly to the 20 test compound, blanching was not observed at concentrations of hydrocortisone below 0.03M. Further, it was noted that 0.03 M hydrocortisone caused approximately the same degree of blanching as that resulting from use of 0.001 M chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate. 20

25 EAR EDEMA TEST
The test animals were Sprague/Dawley rats weighing approximately 150 grams each. In treatment groups, selected amounts of the test compound were dissolved in acetone containing 5% croton oil and 50 microliters of the solution were applied to the inner surface of the right ear of the rats. A control group was identically treated with vehicle only, i.e. 5% croton oil in 30 acetone. Six hours after croton oil challenge, a constant region of each ear was removed by dissection under anesthesia. Then, 48 hours after steroid treatment, the animals were sacrificed and the thymi and adrenals were removed and weighed. The test results showing the inhibitory effect of topically applied steroids on the ear swelling induced by croton oil are summarized in Table II below. 30

TABLE II
Effect of topically applied soft steroid and reference steroids on ear swelling induced by croton oil.

| 5 | Test Compound | Dose ^a mg/kg | Number of Test Animals | Ear Weight (mg) ^b Inflamed Ear | Untreated Ear | 5 |
|----|---|----------------------------|------------------------------|--|----------------------------------|----|
| 10 | None (Control) | | 5 | 75.2±4.5 | 46.6±1.4 | 10 |
| 15 | Chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate | 0.3 1 3 | 5 5 5 | 62.2±3.0* 55.0±2.6** 52.6±1.8** | 50.8±2.4 48.4±1.0 51.6±3.2 | 15 |
| 20 | Hydrocortisone 17-butyrate | 1 | 5 | 50.0±2.3** | 52.0±2.5 | 20 |
| 25 | Betamethasone 17-valerate | 1 | 5 | 55.4±1.2* | 50.4±2.0 | 25 |

a : calculated values based on application of 50 μ l of steroid solution.

b : 50 μ l of 5% croton oil/acetone and drugs in 5% croton oil/acetone were applied to the right ear. Ear weight was measured 6 hr after topical application.

*:p<0.05; **p<0.01: Significant difference from control.

35 TABLE II (continued) 35

| 40 | Test Compound | % Increase | % Inhibition | Relative Organ Weight (mg/100g body wt.) | | 40 |
|----|---|--------------------------------------|----------------------|---|----------------------------------|----|
| | | | | Thymus | Adrenals | |
| 45 | None (Control) | 61.4±8.9 | | 333±15 | 23.3±1.7 | 45 |
| 50 | Chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate | 23.3±7.2* 14.0±6.5** 3.7±8.1** | 62.1 77.2 94.0 | 290±25 293±21 288±21 | 26.0±2.5 18.7±1.4 20.3±0.8 | 50 |
| 55 | Hydrocortisone 17-butyrate Betamethasone 17-valerate | -3.6±3.5** 10.9±6.3** | 106.0 82.2 | 303±21 267±19* | 20.2±0.7 18.9±1.9 | 55 |

*:p<0.05; **p<0.01: Significant difference from control.

As can be seen from Table II above, the representative species of the present invention, namely chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate, substantially inhibited the swelling (and consequent increased weight) of the ear caused by croton oil, i.e., the compound exhibited substantial anti-inflammatory activity. On the other hand, in contrast to the effect caused by betametasone 17-valerate, the representative compound of the invention did not significantly decrease the thymus weight as compared to the control, i.e., it did not show a significant degree of systemic activity.

GRANULOMA FORMATION TEST

The test compound was dissolved in acetone and aliquots of varying concentrations were injected into cotton pellets. The pellets were dried and then one pellet was implanted beneath the skin of each test rat. Six days later, the animals were sacrificed and the granulation tissue (granuloma) which formed in and around the implanted pellet was removed, dried and weighed. In addition, the thymi and adrenals were removed and weighed. The ability of a compound to inhibit granuloma formulation in this test is a direct indication of local anti-inflammatory activity; thus, the lower the weight of granulation tissue, the better the anti-inflammatory activity. On the other hand, a significant decrease in thymus weight is indicative of significant systemic activity; conversely, when a test compound does not significantly decrease thymus weight as compared to the control, such is indicative of a lack of (or very minimal) systemic side effects.

The results are tabulated in Tables III, IV and V-a and V-b below.

TABLE III

Effect of locally administered soft steroids and reference steroids on body weight, thymus weight, and granulation tissue formation caused by implantation of cotton pellets in rats.

| Test Compound | Dose (mg/pellet) | Number of Test Animals | Body wt. gain (g) |
|--|------------------|------------------------|-------------------|
| None (Control) | | 10 | 40.5±0.8 |
| Chloromethyl 17α-ethoxycarbonyloxy-11β-hydroxyandrost-4-en-3-one-17β-carboxylate | 0.1 | 8 | 36.0±2.8 |
| | 0.3 | 8 | 33.0±1.3*** |
| | 1 | 8 | 32.8±0.9*** |
| | 3 | 7 | 30.7±1.5*** |
| Chloromethyl 11β-hydroxy-17α-methoxy-carbonyloxyandrost-4-en-3-one-17β-carboxylate | 1 | 7 | 33.4±1.3*** |
| Hydrocortisone 17-butrate | 1 | 8 | 33.4±1.4*** |
| | 3 | 8 | 15.9±1.4*** |
| | 10 | 8 | 4.9±1.0*** |
| Betamethasone 17-valerate | 1 | 8 | 16.6±1.9*** |
| | 3 | 8 | 14.9±1.7*** |
| | 10 | 8 | 17.0±2.1*** |

*, **, p<0.01

(Mean ± S.E.)

TABLE III continued
Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

| Test Compound | Granulation tissue | | | Relative | |
|---|----------------------------------|-------------------|--------------------|---|----------|
| | Dry wt. (mg/100g body wt.) | Inhibition (%) | Thymus | organ weight mg/100g body wt. (Decrease %) | Adrenals |
| None (Control) | 43.7±4.2 | | 326±22 | 23.7±1.1 | |
| Chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate | 34.7±4.3 | 20.6 | 282±13 (13.5) | 22.9±2.6 (3.4) | |
| | 25.3±2.3** | 42.1 | 298±16 (8.6) | 22.8±1.0 (3.8) | |
| | 14.0±1.8*** | 68.0 | 304±10 (6.7) | 21.8±1.3 (8.0) | |
| | 18.7±2.3*** | 57.2 | 278±21 (14.7) | 19.6±1.1* (17.3) | |
| Chloromethyl 11 β -hydroxy-17 α -methoxy-carbonyloxyandrost-4-en-3-one-17 β -carboxylate | 24.6±2.6** | 43.7 | 218±15** (33.1) | 19.1±1.1** (19.4) | |
| Hydrocortisone | 32.2±5.0 | 26.3 | 73±5 *** (77.6) | 27.1±1.4 (-14.3) | |
| 17-butyrate | 21.6±2.2** | 50.6 | 47±3 *** (85.6) | 16.5±1.2*** (30.4) | |
| | 29.2±3.1* | 33.2 | 32±3 *** (90.2) | 16.8±1.2*** (29.1) | |
| | 35.4±7.3 | 19.0 | 47±2 *** (85.6) | 15.5±1.3*** (34.6) | |
| Betamethasone | | | | | |
| 17-valerate | 31.6±2.1* | 27.7 | 38±3 *** (88.3) | 13.6±0.9*** (42.6) | |
| | 40.7±2.6 | 6.9 | 43±4 *** (86.8) | 12.6±0.9*** (46.8) | |

*p<0.05, **, p<0.01, ***, p<0.001.

(mean±S.E.)

TABLE IV
Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

| Test Compound | Dose (μ g/pellet) | Number of Test Animals | Body wt. gain (g) |
|---|------------------------------|---------------------------|---|
| None (Control) | | 10 | 32.4 \pm 1.4 |
| Chloromethyl 11 β -hydroxy-17 α -isopropoxycarbonyloxy-androst-4-en-3-one-17 β -carboxylate | 100 300 1000 3000 | 8 8 8 8 | 34.9 \pm 2.7 33.9 \pm 1.6 34.0 \pm 2.6 32.4 \pm 2.3 |
| Chloromethyl 11 β -hydroxy-17 α -isopropoxycarbonyloxy-androsta-1,4-dien-3-one-17 β -carboxylate | 30 100 300 1000 | 8 7 8 8 | 32.4 \pm 1.2 35.0 \pm 1.5 34.4 \pm 1.1 29.4 \pm 1.5 |
| Chloromethyl 17 α -ethoxy-carbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 0.3 1 3 10 30 | 8 8 8 8 8 | 32.4 \pm 1.1 37.3 \pm 1.5* 34.3 \pm 1.1 36.1 \pm 1.1 31.3 \pm 1.4 |
| Chloromethyl 9 α -fluoro-11 β -hydroxy-17 α -isopropoxy-carbonyloxy-16 β -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 1 3 10 30 | 7 8 8 8 | 33.0 \pm 1.7 30.4 \pm 1.1 33.0 \pm 1.5 31.8 \pm 1.7 |
| Hydrocortisone 17-butyrate | 300 1000 3000 10000 | 6 6 6 6 | 26.2 \pm 1.7* 26.2 \pm 1.2** 6.7 \pm 2.2*** -2.0 \pm 2.4*** |
| Betamethasone 17-valerate | 100 300 1000 3000 | 7 8 7 8 | 24.9 \pm 1.9** 22.3 \pm 1.2*** 5.3 \pm 1.0*** 6.6 \pm 1.4*** |

* , p<0.05, ** , p<0.01, *** , p<0.001. (Mean \pm S.E.)

TABLE IV continued
Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

| Test Compound | Granulation tissue | | | | Thymus wt. (Decrease %) |
|---|---|--------------------------------------|---|--------------------------------------|---|
| | Wet wt. (mg) | Inhibition (%) | Dry wt. (mg) | Inhibition (%) | |
| None (Control) | 566±28 | | 81.2±6.3 | | 445±20 |
| Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxy-androstan-3-one-17β-carboxylate | 485±36 431±20** 305±16*** 292±7 *** | 14.3 23.9 46.1 48.4 | 70.0±6.0 50.9±2.8** 24.1±2.7*** 20.3±1.3*** | 13.8 37.3 70.3 75.0 | 452±29 469±25 464±30 459±24 |
| Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxy-androsta-1,4-dien-3-one-17β-carboxylate | 432±15** 417±27** 369±18*** 289±12*** | 23.7 26.3 34.8 48.9 | 51.0±2.0** 41.1±5.8*** 38.1±5.9*** 18.5±2.4*** | 37.2 49.4 53.1 77.2 | 523±26* 537±31* 525±28* |
| Chloromethyl 17α-ethoxy-carbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate | 472±23* 388±31*** 331±11*** 313±13*** | 16.6 31.4 41.5 44.7 | 57.3±5.0* 36.4±2.4*** 27.4±2.9*** 22.1±3.6*** | 29.4 55.2 66.3 72.8 | 492±26 519±22* 472±16 521±35 |
| Chloromethyl 9α-fluoro-11β-hydroxy-17α-isopropoxycarbonyloxy-16β-methyl-androsta-1,4-dien-3-one-17β-carboxylate | 290±10 423±19** 351±19*** 362±8 *** 315±12*** | 48.8 25.3 38.0 36.0 44.3 | 20.4±2.4*** 44.4±5.4*** 26.9±4.4*** 29.9±3.3*** 19.9±2.3*** | 74.9 45.3 66.9 63.2 75.5 | 505±26 526±30* 471±20 474±25 489±26 |
| Hydrocortisone | 333±21*** 366±24*** 329±14*** 311±7 *** | 41.2 35.3 41.9 45.1 | 34.0±5.3*** 35.3±4.2*** 28.0±2.7*** 27.2±2.4*** | 58.1 56.5 65.5 66.5 | 353±37* 99±7 *** 58±5 *** 46±7 *** |
| 17-butyrate | 400±19*** 347±15*** 363±28*** 374±15*** | 29.3 38.7 35.9 33.9 | 41.1±2.7*** 33.3±3.6*** 38.1±4.8*** 43.0±4.1*** | 49.4 59.0 53.1 47.0 | 364±24* 264±29*** 77±5 *** 63±3 *** |
| Betamethasone | | | | | (89.7) |
| 17-valerate | | | | | (87.0) |
| | | | | | (18.2) |
| | | | | | (40.7) |
| | | | | | (82.7) |
| | | | | | (85.8) |
| | | | | | (Mean±S.E.) |

*, p<0.05, **, p<0.01, ***, p<0.001.

TABLE V -a
Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

| Test Compound | Dose (μg/pellet) | Number of Test Animals | Body wt. gain (g) |
|---|---------------------------|------------------------|--|
| None (Control) | | 10 | 33.5±1.0 |
| Chloromethyl 17α-ethoxy-9α-fluoro-carbonyloxy-16β-methyl-androsta-1,4-dien-3-one-17β-carboxylate | 0.3 1 3 10 | 8 8 8 8 | 32.5±1.1 36.3±0.9 33.8±1.3 31.1±1.7 |
| Chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-propoxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate | 0.3 1 3 10 | 8 8 7 8 | 35.6±1.0 31.9±0.8 34.1±1.9 33.1±1.6 |
| Betamethasone 17-valerate | 10 30 100 | 6 6 6 | 31.8±1.6 30.8±3.0 25.7±1.2*** |
| Clobetasol 17-propionate | 1 3 10 30 100 | 8 7 8 8 8 | 33.0±1.2 24.9±1.8*** 25.0±2.1*** 24.8±1.1*** 15.9±1.0*** |

* p<0.05, **p<0.01, ***p<0.001.

(Mean±S.E.)

TABLE V-a (continued)
Effect of locally administered soft steroids and reference steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

| Test Compound | Granulation Tissue | | | Thymus wt. (Decrease %) |
|---|---|--------------------------------------|--|--------------------------------------|
| | Wat wt. (mg) | Inhibition (%) | Dry wt. (mg) | |
| None (Control) | 525±19 | 80.1±5.1 | 495±36 | |
| Chloromethyl 17 α -ethoxy- carbonyloxy-9 α -fluoro- 11 β -hydroxy-16 β -methyl-1- androsta-1,4-dien-3-one- 17 β -carboxylate | 499±36 437±24* | 5.0 16.8 | 61.8±5.7* 57.0±6.2* | 22.8 28.0 |
| Chloromethyl 9 α -fluoro-11 β - hydroxy-16 α -methyl-17 α - propanoylcarnboxyloxyandrosta- 1,4-dien-3-one-17 β - carboxylate | 454±27* 415±30** 360±18*** 350±13*** | 13.5 21.0 31.4 33.3 | 55.1±6.2** 42.9±5.1*** 29.7±3.2*** 28.5±2.8*** | 31.2 46.4 62.9 64.4 |
| Betamethasone 17-valerate | 375±19*** 412±42** 419±20** | 28.6 21.5 20.2 | 38.5±6.2*** 46.2±7.4** 41.0±4.2*** | 51.9 42.3 48.8 |
| Clobetasol 17-propionate | 401±29** 402±40** 364±25*** 320±10*** 325±12*** | 23.6 23.4 30.7 39.0 38.1 | 42.0±5.8*** 43.1±8.9** 37.9±6.8*** 25.5±2.1*** 23.9±3.3*** | 47.6 46.2 52.7 68.2 70.2 |

* , p < 0.05, ** , p < 0.01, *** , p < 0.001.

(Mean±S.E.)

Table V-b

Effect of locally administered soft steroids on body weight, thymus weight and granulation tissue formation caused by implantation of cotton pellets in rats.

| Test Compound | Dose (ug/pellet) | Number of Test animals | Body wt. gain (g) | Dry granulation Tissue Inhibition % | Thymus wt. mg |
|---|---------------------|------------------------------|----------------------|--|------------------|
| None (Control) | — | 10 | 28.0 \pm 1.5 | 67.2 \pm 3.4 | 505 \pm 22 |
| Chloromethyl 9 α -fluoro-17 α -isopropoxycarbonyloxy-16 β -methylandrosta-1,4-dien-3,11-dione-17 β -carboxylate | 1 | 8 | 28.9 \pm 1.1 | 59.1 \pm 5.8 | 12.1 |
| | 3 | 8 | 25.8 \pm 0.9 | 49.4 \pm 3.7** | 26.5 |
| | 10 | 7 | 28.4 \pm 0.8 | 51.1 \pm 5.8* | 24.0 |
| | 30 | 8 | 27.4 \pm 0.9 | 40.6 \pm 3.6*** | 39.6 |
| Chloromethyl 17 α -ethoxy-carbonyloxy-9 α -fluoro-16 β -methylandrosta-1,4-dien-3,11-dione-17 β -carboxylate | 1 | 7 | 23.7 \pm 1.5 | 55.3 \pm 2.6* | 17.7 |
| | 3 | 8 | 25.6 \pm 1.2 | 51.6 \pm 5.9* | 23.2 |
| | 10 | 8 | 26.5 \pm 2.5 | 41.5 \pm 4.7*** | 38.2 |
| | 30 | 8 | 20.3 \pm 0.9** | 39.9 \pm 3.6*** | 40.6 |

*, p 0.05, **, p 0.01, ***, p 0.001.
(Mean \pm S.E.)

Male Sprague-Dawley rats, weighing 152-189g (mean body weight 171g), were used.
Cotton pellet weight was 30.1 \pm 0.3 mg (number of test animals were 30).

- The test data in Tables III, IV and V-a and V-b above clearly show that the representative compounds of the present invention exhibited a significant anti-inflammatory response at lower dosages than did the prior art steroids, hydrocortisone 17-butyrate and betamethasone 17-valerate. On the other hand, all of the prior art steroids dramatically decreased the weight of the thymi and thus showed very potent systemic activity, while the representative compounds of the invention either did not significantly decrease the thymi weights or only minimally decreased the thymi weight. Thus, the present compounds have a much greater therapeutic index, i.e., separation of local anti-inflammatory from systemic activity, than do the prior art steroidal anti-inflammatory agents. 5
- 10 Also the test data in Table V-b above shows that the representative compounds of the present invention exhibited a significant local anti-inflammatory activity.
- From the results tabulated in Tables IV and V-b, the ED₄₀'s, ED₅₀'s and ED₆₀'s and the relative potencies of representative compounds of the invention were calculated and are shown in Table VI below. One of the compounds of the invention, namely chloromethyl 11-hydroxy-17-isopropoxycarbonyloxyandrost-4-en-3-one-17-carboxylate, has been assigned a potency value of 15 1 at each ED level, and the potencies of the other compounds are expressed relative thereto. The ED₄₀'s, ED₅₀'s and ED₆₀'s are the dosages required to achieve, respectively, 40%, 50% and 60% reduction in the weight of the granulation tissue. 10

TABLE VI
Relative potencies of soft steroids in the local cotton pellet granuloma assay.

| Test Compound | ED ₄₀ ($\mu\text{g}/\text{pellet}$) | Relative potency | ED ₅₀ ($\mu\text{g}/\text{pellet}$) | Relative potency | ED ₆₀ ($\mu\text{g}/\text{pellet}$) | Relative potency |
|--|---|-----------------------|---|---------------------|---|---------------------|
| Chloromethyl 11 β -hydroxy-17 α -isopropoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylate | 307 (238-394) | 1 | 460 (360-623) | 1 | 690 (523-1023) | 1 |
| Chloromethyl 11 β -hydroxy-17 α -isopropoxycarbonyloxyandrost-1,4-dien-3-one-17 β -carboxylate | 47 | 6.5 | 119 (60-202) | 3.9 | 301 (178-627) | 2.3 |
| Chloromethyl 17 α -ethoxy-carbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 0.47 | 653 (0.23-0.75) | 1.07 (0.66-1.59) | 430 (0.08-2.31) | 2.44 (1.65-3.86) | 283 |
| Chloromethyl 9 α -fluoro-11 β -hydroxy-17 α -isopropoxycarbonyloxy-16 β -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 0.25 | 1228 (0.004-0.886) | 0.97 (2.96-44.58) | 474 (6.47-393.8) | 3.75 (1.25-7.68) | 184 |
| Chloromethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 β -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 2.31 (1.07-6.38) | 133 | 6.45 (0.67-2.88) | 71 (1.37-13.32) | 18.01 (1.37-13.32) | 38 |
| Chloromethyl 9 α -fluoro-11 β -hydroxy-16 α -methyl-17 α -propoxycarbonyloxyandrost-1,4-dien-3-one-17 β -carboxylate | 0.58 (0.20-1.01) | 529 | 1.20 (0.67-2.88) | 383 (1.37-13.32) | 2.49 (1.37-13.32) | 277 |
| Hydrocortisone 17-butyrate | — | — | — | — | 1.015 (724-26866) | 0.7 |
| Clobetasol 17-propionate | — | — | >3 (724-26866) | >10 (724-26866) | — | — |

1 dose causing 40% inhibition of granulation tissue weight.

2 dose causing 50% inhibition of granulation tissue weight.

3 dose causing 60% inhibition of granulation tissue weight.

() = 95% confidence limits

THYMUS INHIBITION TESTING

Several further studies were undertaken to determine the effects of selected compounds of the invention on thymi weights in rats when the drugs were systemically administered. In each of these studies, male Sprague-Dawley rats were used. (For average weight of rats for each study, see the tables which follow.) The test compounds were suspended in 0.5% CMC (carboxymethylcellulose) and injected subcutaneously once daily for three days. On the fifth day (48 hours following the last treatment), the animals were sacrificed and the thymi weights were recorded. Body weight gains were measured 24 hours after the last treatment. The test results are set forth in Tables VII, VIII and IX below. The TED₄₀'s, TED₅₀'s (thymolytic effective doses or doses required to achieve 40% and 50% inhibition of thymi weight, respectively) and relative potency of representative compounds of the invention and reference steroids are shown in Table X below. In Table X, the TED₄₀ and TED₅₀ for the reference steroid betamethasone 17-valerate has each been assigned a value of 1, and the potencies of the other compounds are expressed relative thereto. It is evident that the higher the inhibition of thymus activity at a given dose, the more toxic the compound is.

5

10

15

TABLE VII
Effects of systemically administered (s.c.) soft steroids and reference steroids on body weight and thymus weight in rats.

| Test Compound | Dose (mg/kg/day) | Number of Test Animals | Body weight gain (g) | Thymus (mg) | Inhibition (%) |
|--|------------------|------------------------|--|---|---------------------|
| None (Control) | | 9 | 18.3±0.7 | 471±21 | |
| Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxy-androst-4-en-3-one-17β-carboxylate | 3 10 30 100 | 9 10 10 10 | 14.7±0.6** 10.2±0.7*** 6.8±2.1*** 2.8±1.8*** | 439±18 386±17** 291±22*** 185±17*** | 6.8 18.0 38.2 60.7 |
| Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyl-oxyandrosta-1,4-dien-3-one-17β-carboxylate | 3 10 30 100 | 9 9 10 10 | 9.0±0.9*** 6.2±0.7*** 4.8±1.4*** 0.3±1.6*** | 377±16** 312±23*** 257±24*** 161±19*** | 20.0 33.8 45.4 65.8 |
| Chloromethyl 17α-ethoxy-carbonyloxy-9α-fluoro-11β-hydroxy-16α-methyl-androsta-1,4-dien-3-one-17β-carboxylate | 1 3 10 30 | 10 9 10 10 | 13.1±1.0*** 12.7±1.4** 9.7±1.3*** 4.4±0.7*** | 428±20 41.2±20 405±21* 292±15*** | 9.1 12.5 14.0 38.0 |
| Hydrocortisone | 0.3 | 10 | 17.0±0.8 | 441±27 | 6.4 |
| 17-butyratate | 1 3 10 | 10 10 10 | 11.8±0.8*** 7.3±0.5*** -5.0±1.1*** | 323±16*** 166±5 *** 65±5 *** | 31.4 64.8 86.2 |
| Betamethasone | 0.1 0.3 1 3 | 10 10 10 10 | 15.5±0.9* 12.4±0.9*** 13.0±1.1*** 9.9±1.3*** | 362±16*** 276±11*** 200±14*** 119±7 *** | 23.1 41.4 57.5 74.7 |

* p<0.05, ** p<0.01, *** p<0.001

Male Sprague-Dawley rats, weighing 149-168g, were used.

(Mean±S.E.)

TABLE VIII
Effects of systemically administered (s.c.) soft steroids and reference steroids on body weight and thymus weight in rats.

| Test Compound | Dose (mg/kg/day) | Number of Test Animals | Body weight gain (g) | Thymus wt. (mg) | Inhibition (%) |
|---|---------------------|---------------------------|-------------------------|--------------------|-------------------|
| None (Control) | | 10 | 18.9±0.6 | 550±24 | |
| Chloromethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methyl-androsta-1,4-dien-3-one-17 β -carboxylate | 10 | 7 | 14.2±1.9 | 533±31 | 3.1 |
| Chloromethyl 9 α -fluoro-11 β -hydroxy-17 α -isopropoxycarbonyloxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 10 | 7 | 2.7±1.9*** | 234±31*** | 57.5 |
| Chloromethyl 9 α -fluoro-11 β -hydroxy-17 α -isopropoxycarbonyloxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 10 | 7 | 5.3±1.4*** | 260±26*** | 52.7 |
| Chloromethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 β -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 10 | 7 | 2.4±1.8*** | 266±20*** | 51.6 |
| Chloromethyl 17 α -ethoxycarbonyloxy-16 α -methyl-17 β -hydroxy-11 β -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 10 | 7 | 2.7±1.7*** | 277±25*** | 49.6 |
| Clobetasol 17-propionate | 0.003 | 8 | 18.2±0.6 | 537±28 | 2.4 |
| | 0.01 | 8 | 15.5±1.1* | 498±15 | 9.5 |
| | 0.03 | 8 | 12.3±1.3** | 363±22*** | 34.0 |
| | 0.1 | 8 | -0.4±1.3*** | 149±9 *** | 72.9 |
| | 0.3 | 8 | -14.3±1.3*** | 63±3 *** | 88.5 |

* p<0.05, ** p<0.01, *** p<0.001.
(mean±S.E.)

Male Sprague-Dawley rats, weighing about 185g (162-209g), were used.

TABLE IX
Effects of systemically administered (s.c.) soft steroids on body weight and thymus weight in rats.

| Test Compound | Dose (mg/kg/day) | Number of Test Animals | Body weight gain (g) | Thymus wt. (mg) | Decrease (%) |
|---|----------------------|---------------------------|--|--|-----------------------------|
| None (Control) | | 10 | 21.2±0.9 | 426±17 | |
| Chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate | 3 10 30 100 | 7 7 7 7 | 18.8±1.4 13.8±1.6*** 12.0±0.8*** 9.8±1.3*** | 426±19 354±8 ** 282±11*** 206±15*** | 0.0 16.9 33.8 51.6 |
| Chloromethyl 9α-fluoro-11β-hydroxy-16α-methyl-17α-pentyloxycarbonyloxyandrosta-1,4-dien-3-one-17β-carboxylate | 1 3 10 30 | 7 7 7 7 | 18.0±1.5 15.6±1.3** 17.4±1.5* 13.5±1.0*** | 387±23 347±15** 357±22* 335±17** | 9.2 18.5 16.2 21.4 |

* , p<0.05, ** , p<0.01, *** , p<0.001
 (Mean±S.E.)

Male Sprague-Dawley rats, weighing 91-112g, were used.

TABLE X
Thymolytic activities of soft steroids administered subcutaneously to rats.

| Compound | TED ₄₀ (mg) | Relative Potency | TED ₅₀ (mg) | Relative Potency |
|---|---------------------------|---------------------|---------------------------|---------------------|
| Chloromethyl 11 β -hydroxy-17 α -isopropoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylate | 31.0 (23.9-41.9) | 0.01 | 58.5 (43.1-87.1) | 0.01 |
| Chloromethyl 11 β -hydroxy-17 α -isopropoxycarbonyloxyandrost-1,4-dien-3-one-17 β -carboxylate | 16.2 (11.2-23.2) | 0.02 | 35.3 (24.6-57.5) | 0.02 |
| Chloromethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 51.5 (26.5-290.0) | 0.0058 | > 51.5 ^a | <0.011 |
| Hydrocortisone 17-butyrate | 1.3 (1.1-1.5) | 0.23 | 2.0 (1.7-2.3) | 0.29 |
| Betamethasone 17-valerate | 0.30 (0.24-0.36) | 1 | 0.58 (0.49-0.69) | .1 |
| Clobetasol 17-propionate | 0.035 (0.030-0.039) | 8.6 | 0.052 (0.046-0.059) | ..11.2 |

^a Even at a dosage level of 100 mg/kg/day, 50% reduction in thymus weight could not be achieved.

BLANK COTTON PELLET GRANULOMA ASSAY

A further test was undertaken to determine the thymolytic activity of a representative species of the invention as compared to betamethasone 17-valerate. In this test, the drugs were administered intravenously to rats, while using a blank cotton pellet granuloma assay. Male

- 5 Sprague-Dawley rats, each weighing about 185 grams (166–196 grams), were used. Two cotton pellets, each weighing 30 mg and containing no test compounds, were sterilized and implanted subcutaneously into the back of each test animal. This day was considered day 0 of implantation. Test compounds suspended in 0.8% polysorbate 80 were administered intravenously once daily for 3 consecutive days beginning with day 1. On day 5, the animals were 10 sacrificed and the two pellets, with their respective granulomas, were removed, dried overnight in an oven at 50°C and weighed (dry granuloma weight). The thymi and final body weights were also recorded. The results are given in Table XI below.

In the foregoing tests, there was determined the deactivation of representative species of present soft steroids administered intravenously to rats. The ratio between the potencies of the 15 test steroids and betamethasone 17-valerate against local anti-inflammation was 283:0.7 as seen from Table VI. This means that the test compounds exhibit a local anti-inflammatory activity which is approximately 400 times as high as the activity of the betamethasone 17-valerate. The test compounds were administered intravenously to rats to check the test compounds also for systemic anti-inflammatory activity as compared to betamethasone 17-valerate. The test compounds were found lower in the inhibition of granulation tissue formation 20 and also in the thymus involution activity than betamethasone 17-valerate. From the results of the tests, it is presumed that the compounds which will not be readily subjected to metabolism (deactivation) have a systemic anti-inflammatory activity, as is the case with betamethasone 17-valerate.

TABLE XI
Thymolytic activities of test steroids administered intravenously to rats in the blank cotton pellet granuloma assay.

| Test Compound | Dose (mg/kg/day) | Number of Test Animals | Body wt. gain (g) | Dry granuloma wt. (mg) | Inhibition (%) | Thymus wt. (mg) | Decrease (%) |
|---|----------------------|---------------------------|---|--|------------------------------|---|------------------------------|
| None (Control) | | 7 | 21.4±1.3 | 62.7±6.1 | | 422±27 | |
| Chloromethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 1 | 7 | 14.1±1.4** | 50.1±6.9 | 20.1 | 373±25 | 11.6 |
| | 3 | 6 | 14.2±1.3** | 49.3±5.1 | 21.4 | 338±20* | 19.9 |
| | 10 | 6 | 0.3±1.7*** | 45.7±4.6 | 27.1 | 209±31*** | 50.5 |
| | 30 | 6 | -18.5±2.3*** | 32.7±3.0* | 47.8 | 71±4 *** | 83.2 |
| Betamethasone 17-valerate | 0.1 0.3 1 3 | 7 5 7 7 | 14.4±1.6** 12.2±1.1*** 12.9±1.1*** 13.0±2.5* | 49.3±3.9 44.4±2.8* 46.1±4.3* 47.3±2.7 | 21.4 29.2 26.5 24.6 | 305±14** 288±27*** 233±15*** 167±22*** | 27.7 31.8 44.8 60.4 |

* , p<0.05, ** , p<0.01, *** , p<0.001.
 (Mean±S.E.)

The ED₅₀'s calculated for the local cotton pellet granuloma assay (as shown, for example, in Table VI above) and the TED₄₀'s calculated on the basis of thymus inhibition testing (as shown, for example, in Table X above) were used to arrive at relative potency and a therapeutic index for representative species of the invention as compared to prior art steroids. See Table XII below, which clearly shows the potent anti-inflammatory activity and minimal systemic toxicity of the compounds of the present invention. 5

TABLE XII

| Compound | ED ₅₀ ^a | Relative Potency | TED ₄₀ ^b | Relative Potency | Therapeutic Index ^c |
|---|-------------------------------|------------------|--------------------------------|------------------|--------------------------------|
| Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-4-en-3-one-17β-carboxylate | 460 (360-623) | 1 | 31.0 (23.9-41.9) | 1/24 | 24 |
| Chloromethyl 11β-hydroxy-17α-isopropoxycarbonyloxyandrost-1,4-dien-3-one-17β-carboxylate | 119 (60-202) | 4 | 16.2 (11.2-23.2) | 1/12 | 48 |
| Chloromethyl 17α-ethoxycarbonyloxy-9α-fluoro-11β-hydroxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate | 1.07 (0.66-1.59) | 450 | 51.5 (26.5-290.0) | 1/40 | 18000 |
| Chloromethyl 9α-fluoro-11β-hydroxy-17α-methoxycarbonyloxy-16α-methylandrosta-1,4-dien-3-one-17β-carboxylate | 2.38 (1.60-3.78) | 202 | 46.0 (36.0-62.1) | 1/36 | 7270 |
| Hydrocortisone 17-butyrate | 480 (313-892) | 1 | 1.3 (1.1-1.5) | 1 | 1 |
| Betamethasone 17-valerate | 100 | 5 | 0.3 (0.24-0.36) | 4 | 1 |

^afor the anti-inflammatory effect in cotton pellet granuloma (μg/pellet)

^bfor the thymus inhibition effect required subcutaneously (mg/kg)

^cthe ratio of the relative potency for the ED₅₀ to the relative potency for the TED₄₀^b
hydrocortisone 17-butyrate has been assigned a value of one

The compounds of formula (I) can be combined with suitable non-toxic pharmaceutically acceptable carriers to provide pharmaceutical compositions for use in the treatment of topical or other localized inflammation. Obviously, in view of their lack of systemic activity, the compounds of the present invention are not intended for treatment of conditions where systemic

- 5 adrenocortical therapy is indicated, e.g., adrenocortical insufficiency. As examples of inflammatory conditions which can be treated with pharmaceutical compositions containing at least one compound of the invention and one or more pharmaceutical carriers, the following can be mentioned: dermatological disorders such as atopic dermatitis, acne, psoriasis or contact dermatitis; allergic states such as bronchial asthma; ophthalmic and otic diseases involving acute 5
10 and chronic allergic and inflammatory reactions; respiratory diseases; ulcerative colitis; and anorectal inflammation, pruritus and pain associated with hemorrhoids, proctitis, cryptitis, fissures, postoperative pain and pruritus ani. Such compositions may also be applied locally as a prophylactic measure against the inflammation and tissue rejection which arise in connection with transplants.

- 15 Obviously, the choice of carrier(s) and dosage forms will vary with the particular condition for which the composition is to be administered.

- Examples of various types of preparations for topical/local administration include ointments, lotions, creams, powders, drops, (e.g. eye or ear drops), sprays, (e.g. for the nose or throat), suppositories, retention enemas, chewable or suckable tablets or pellets (e.g. for the treatment 20
20 of aphthous ulcers) and aerosols. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or glycols. Such base may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil, or a glycolic solvent such as propylene glycol or 1,3-butanediol. Thickening agents which may be used according to the nature of the base 25
25 include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, woolfat, hydrogenated lanolin and beeswax and/or glycetyl monostearate and/or non-ionic emulsifying agents.

- The solubility of the steroid in the ointment or cream may be enhanced by incorporation of an aromatic alcohol such as benzyl alcohol, phenylethyl alcohol or phenoxyethyle alcohol.

- 30 Lotions may be formulated with an aqueous or oily base and will in general also include one or more of the following, namely, emulsifyin agents, dispensing agents, suspending agents, thickening agents, solvents, coloring agents and perfumes. Powders may be formed with the aidof any suitable powder base e.g. talc, lactose or starch. Drops may be formulated with an aqueous base also comprising one or more dispersing agents, suspending agents or solubilizing 35
35 agents, etc. Spray compositions may, for example, be formulated as aerosols with the use of a suitablepropellane, e.g., dichlorodifluromethane or trichlorofluoromethane.

- The proportion of active ingredient in the compositions according to the invention will vary with the precise compound used, the type of formulation prepared and the particular condition for which the composition is to be administered. The formulation will generally contain from 40 about 0.0001 to about 5.0% by weight of the compound of formula (I). Topical preparations will generally contain 0.0001 to 2.5%, preferably 0.01 to 0.5%, and will be administered once daily, or as needed. Also, generally speaking, the compounds of the invention can be incorporated into topical and other local compositions formulated substantially as are such presently available types of compositions containing known glucocorticosteroids, at approxi-

- 45 mately the same (or in the case of the most potent compounds of the invention, at proportionately lower) dosage levels as compared to known highly active agents such as methyl prednisolone acetate and beclomethasone dipropionate or at considerably lower dosage levels as compared to less active known agents such as hydrocortisone.

- Thus, for example, an inhalation formulation suitable for use in the treatment of asthma can 50 be prepared as a metered-dose aerosol unit containing a representative species of the invention such as chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate, according to procedures well-known to those skilled in the art of pharmaceutical formulations. Such an aerosol unit may contain a microcrystalline suspension of the aforementioned compound in suitable propellants (e.g., 55
55 trichlorofluoromethane and dichlorodifluoromethane), with oleic acid or other suitable dispersing agent. Each unit typically contains 10 milligrams of the aforesaid active ingredient, approximately 50 micrograms of which are released at each actuation. When one of the more potent species of the invention, e.g. chloromethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate, is employed, each unit typically contains 1 milligram of the active ingredient and releases approximately 5 micrograms at each actuation.

- 60 Another example of a pharmaceutical composition according to the invention is a foam suitable for treatment of a wide variety of inflammatory anorectal disorders, to be applied anally or perianally, comprising 0.1% of a compound of formula (I) such as chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate, and 1% of a local anaesthe- 65
65 tic such as pramoxine hydrochloride, in a mucoadhesive foam base of propylene glycol,

ethoxylated stearyl alcohol, polyoxyethylene-10-stearyl ether, cetyl alcohol, methyl paraben, propyl paraben, triethanolamine, and water, with inert propellents. When a more potent compound of the invention is employed, less active ingredient generally is used, e.g. 0.05% of chloromethyl 9 α -fluoro-11 β -hydroxy-17 α -methoxycarbonyloxy-16 α -methylandrosta-1,4-dien-3-

5 one-17 β -carboxylate.

Yet another pharmaceutical formulation according to the invention is a solution or suspension suitable for use as a retention enema, a single dose of which typically contains 40 milligrams of a compound of the invention such as chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrostan-4-en-3-one-17 β -carboxylate (or 20 milligrams of a more potent compound of the invention such 10 as chloromethyl 9 α -fluoro-11 β -hydroxy-17 α -isopropoxycarbonyloxy-16 β -methylandrosta-1,4-dien-3-one-17 β -carboxylate or chloromethyl 9 α -fluoro-11 β -hydroxy-16 α -methyl-17 α -propoxycarbonyloxyandrosta-1,4-dien-3-one-17 β -carboxylate) together with sodium chloride, polysorbate 80 and from 1 to 6 ounces of water (the water being added shortly before use). The suspension can be administered as a retention enema or by continuous drip several times weekly in the 15 treatment of ulcerative colitis.

Other pharmaceutical formulations according to the invention are illustrated in the examples which follow.

Without further elaboration, it is believed that one of ordinary skill in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the following 20 examples are to be construed as merely illustrative and not limitative of the remainder of the specification and claims in any way whatsoever.

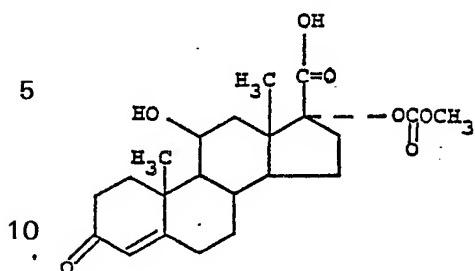
EXAMPLE 1

To a solution of hydrocortisone (15 grams, 0.04 mol) in 120 milliliters of tetrahydrofuran and 25 30 milliliters of methanol at room temperature is added a warm (approximately 50°C) solution of sodium metaperiodate (25.7 grams, 0.12 mol) in 100 milliliters of water. The reaction mixture is stirred at room temperature for 2 hours, then is concentrated under reduced pressure to remove the tetrahydrofuran and methanol. The solid is triturated with 50 milliliters of water, separated by filtration, washed with water and dried *in vacuo* at 50°C for 3 hours. The product, 30 11 β , 17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylic acid (i.e., cortienic acid), melts at 231–234°C, is obtained in approximately 96% yield (13.76 grams), and can be represented by the structural formula



EXAMPLE 2

To a cold solution of 11 β , 17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylic acid (5% weight/volume; 1 mol) and triethylamine (4 mol) in dichloromethane is added a 50% (weight/volume) solution of methyl chloroformate (3.9 mol) in dichloromethane. The reaction mixture is allowed to warm to room temperature over a 2 hour period. The triethylamine hydrochloride precipitate which forms is removed by filtration and the filtrate is washed successively with 3% sodium bicarbonate, dilute (~1%) hydrochloric acid and water. The 50 organic layer is separated, dried with magnesium sulfate, and filtered. The filtrate is concentrated *in vacuo* to a foam. The foam is used in the next step (e.g., Example 3 below) or chromatographed and crystallized for analysis. The product, 11 β -hydroxy-17 α -methoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylic acid, melts at 198–204°C after chromatography and crystallization; ir (KBr) 3000–2800 (C–H), 1750, 1735, 1720 (C=O), 1650, 1640 55 60 (C=C–C=O)cm⁻¹. The product can be represented by the structural formula



- 15 Substitution of an equivalent quantity of ethyl chloroformate for the methyl chloroformate employed above and substantial repetition of the foregoing procedure affords 17α -ethoxycarbonyloxy- 11β -hydroxyandrost-4-en-3-one- 17β -carboxylic acid, melting at 192–195°C after chromatography and crystallization; ir (KBr) 3500 (11 β -O-H), 3000–2800 (C-H), 1740 (C=O), 1630 (C=C-C=O)cm⁻¹; nmr (CDCl₃) δ6.4(1, b, COOH), 5.67(1,s,C=CH), 4.43 (1,b,
20 CHO), 4.13 (2, q, J = 7.5Hz, OCH₂CH₃); Anal. calcd. for C₂₃H₃₂O₇: C, 65.69; H, 7.67. Found: 20 C, 65.76; H, 7.74.

In a similar manner, substitution of an equivalent quantity of butyl chloroformate for the methyl chloroformate employed in the first paragraph of this example and substantial repetition of the procedure there detailed affords 17α -butoxycarbonyloxy- 11β -hydroxyandrost-4-en-3-one-

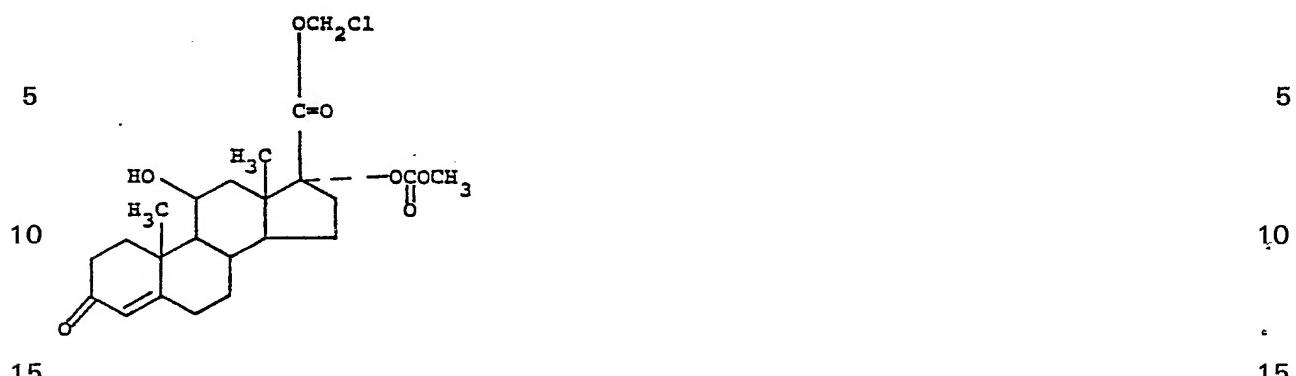
- 25 17 β -carboxylic acid. The final product, after crystallization from tetrahydrofuran-hexane, melts at 25
164–166°C.

Similarly, substituting an equivalent amount of isopropyl chloroformate for the methyl chloroformate used in the first paragraph of this example and repeating the procedure there detailed affords 11 β -hydroxy-17 α -isopropoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylic acid.

- 30 The final product, after crystallization from tetrahydrofuran-hexane, melts at 144.5–146.5°C. 30

EXAMPLE 3

11 β -Hydroxy-17 α -methoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylic acid is combined with an equivalent amount of 1*N* sodium hydroxide in methanol and that solution is diluted to 35 100 times the original volume with ethyl ether. The suspension which results is refrigerated for 1 hour. Then, the crystals which form are removed by filtration, dried in an evacuated desiccator, and dissolved in hexamethylphosphoramide (10% weight/volume). A portion of the resultant solution containing 1 mole of the acid salt, i.e. of sodium 11 β -hydroxy-17 α -methoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylate, is combined with 4 moles of chlorome- 40 thyl iodide. The reaction mixture is maintained at room temperature for 3 hours, then is diluted to 10 times the original volume with ethyl acetate. The diluted reaction mixture is washed successively with 5% sodium thiosulfate, 3% sodium bicarbonate, and water. The organic layer is separated, dried with magnesium sulfate and filtered. The filtrate is concentrated *in vacuo* to a foam. The foam is purified by crystallization from a suitable solvent (ethyl ether or tetrahydrofuran/hexane). There is thus obtained chloromethyl 11 β -hydroxy-17 α -methoxycarbonyloxyandrost- 45 4-en-3-one-17 β -carboxylate, melting at 171–173°C after crystallization; ir (KBr) 3000–2800 (C=H), 1760, 1748 (C=O), 1650 (C=C=O)cm⁻¹; nmr (CDCl₃) δ 5.67 (s, 1, C=CH), 5.82, 5.62 (ABq, J = 5.5Hz, 2, OCH₂Cl), 4.47 (b, 1, CHOH); Anal. calcd. for C₂₃H₃₁ClO: C, 60.72; H, 6.87; Cl, 7.79. Found: C, 60.50; H, 7.06; Cl, 7.50. The product is characterized by 50 the structural formula



Substitution of an equivalent quantity of 17α -ethoxycarbonyloxy- 11β -hydroxyandrost-4-en-3-one- 17β -carboxylic acid for the steroidal acid employed above and substantial repetition of the foregoing procedure affords, as the intermediate salt, sodium 17α -ethoxycarbonyloxy- 11β -

- 19 ongoing procedure affords, as the intermediate salt, sodium 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate, and, as the final product, chloromethyl 17 α -ethoxy-carbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate, melting at 197–200°C after crystallization; ir (KBr) 3600–3200 (O–H), 3000–2800 (C–H), 1763, 1740 (C = O), 1650 (C = C–C = O) cm^{−1}; nmr (CDCl₃) δ 5.7 (s, 1, C = CH), 5.81, 5.62 (ABq, J = 5Hz, 2, –OCH₂Cl); Anal calcd. for C₂₄H₃₃ClO₇: C, 61.46; H, 7.09. Found: C, 61.58; H, 7.08.

20 25 In a similar manner, substitution of an equivalent quantity of 17 α -butoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylic acid for the steroidial acid employed in the first paragraph of this example and substantial repetition of the procedure there detailed affords, as the intermediate salt, sodium 17 α -butoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate, and, as the final product, chloromethyl 17 α -butoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate, melting at 98–100°C after crystallization; ir(KBr) 3600–3300 (O–H), 3000–2800 (C–H), 1765 (O₂C = O), 1735 (OC = O), 1650 (C = C–C = O)cm^{−1}; nmr (CDCl₃) δ 85.80, 85.60 (2, ABq, J = 4.5Hz, –OCH₂Cl), 5.67 (1, s, C = CH), 4.45 (1, b, CHO), 4.08 (2, t, J = 6Hz, O₂COCH₂–CH₂); Anal calcd. for C₂₆H₃₇ClO₇: C, 62.77; H, 7.44; Cl, 7.14. Found: C, 62.88; H, 7.23; Cl, 7.30.

30 35 Similarly, substituting an equivalent amount of 11 β -hydroxy-17 α -isopropoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylic acid for the steroidial acid employed in the first paragraph of this example and substantial repetition of the procedure there detailed affords, as the intermediate salt, sodium 11 β -hydroxy-17 α -isopropoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylate, and, as the final product, chloromethyl 11 β -hydroxy-17 α -isopropoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylate, melting at 183.5–184.5°C after recrystallization from tetrahydronaphthalene-hexane.

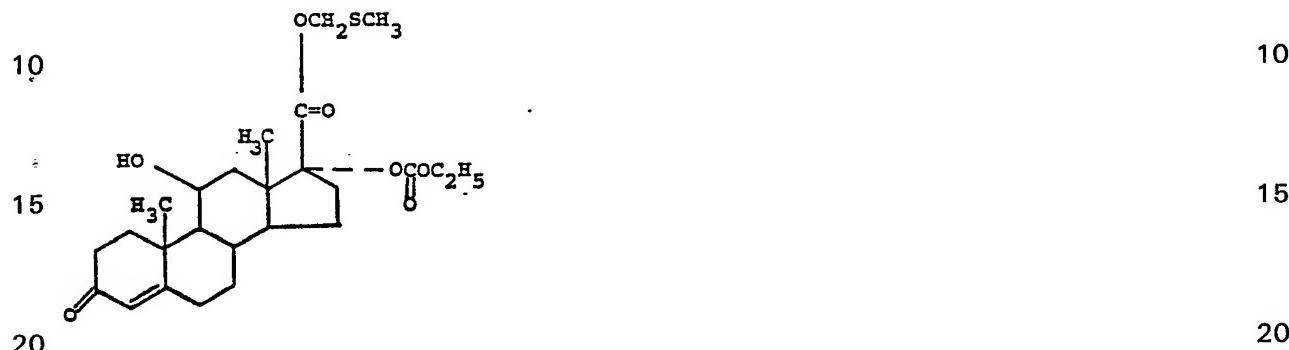
In a similar manner, an equivalent quantity of 17α -ethoxycarbonyloxy- 11β -hydroxyandrost-4-en-3-one- 17β -carboxylic acid is substituted for the steroid acid and an equivalent quantity of butyl chloride is substituted for the chloromethyl iodide employed in the first paragraph of this

- example, and the procedure there detailed is substantially repeated, except that the step of washing with 5% sodium thiosulfate is eliminated. Obtained in this manner are the intermediate salt, sodium 17α -ethoxycarbonyloxy- 11β -hydroxyandrost-4-en-3-one- 17β -carboxylate, and the final product, butyl 17α -ethoxycarbonyloxy- 11β -hydroxyandrost-4-en-3-one- 17β -carboxylate. The final product after crystallization from acetone melts at 148–149°C; after chromatography and crystallization, ir(KBr) 3600–3200 (O—H), 3000–2800 (C—H), 1750 (2 C = O), 1670 (C = C—C = O) cm^{−1}; nmr (CDCl₃) δ5.64 (s, 1, —C = CH), 4.46 (b, 1, CHOH), 4.32–4.95 (m, 4, COOCH₂CH₃⁺, COOCH₂CH₂—); Anal. calcd. for C₂₇H₄₀O₇: C, 67.99; H, 8.39. Found: C, 67.76; H, 7.74.

55 EXAMPLE 4

17 α -Ethoxycarbonyloxy-11 β -hydroxyandrostan-4-en-3-one-17 β -carboxylic acid (3 grams, 7.13 mmol) is treated with 7.13 milliliters of 1M methanolic sodium hydroxide solution, and 500 milliliters of ethyl ether are then added to effect precipitation. The precipitate is separated by filtration and dried in an evacuated dessicator overnight to afford 2.71 grams (6.12 mmol) of the desired salt, i.e. sodium *17 α -ethoxycarbonyloxy-11 β -hydroxyandrostan-4-en-3-one-17 β -carboxylate*, as a yellow powder. The salt is dissolved in 40 milliliters of hexamethylphosphoramide and chloromethyl methyl sulfide (2.36 grams, 24.5 mmol) is added slowly. A precipitate of sodium chloride forms in the reaction mixture within 1 minute. The reaction mixture is stirred at room temperature for 1 hour, then is diluted with ethyl acetate to a total volume of 200 milliliters and washed successively with 3% sodium bicarbonate and water. The organic layer is

separated, dried with magnesium sulfate and filtered. The filtrate is concentrated *in vacuo* to an oil, and the oil is chromatographed from silica gel, using ethyl acetate, chloroform and acetic acid as eluants. The chromatographed product is crystallized from a mixture of ethyl ether and hexane to give white powdery crystals of methylthiomethyl 17 α -ethoxycarbonyloxy-11 β -hydroxy-5 androst-4-en-3-one-17 β -carboxylate, melting at 133–136°C. That product is characterized by the structural formula



To a solution of methylthiomethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate (0.48 gram, 1 mmol) in 2 milliliters of dichloromethane is added *m*-chloroperoxybenzoic acid (0.4 gram = 0.34 gram of peracid, 2 mmol). An exothermic reaction ensues, which subsides quickly. The reaction mixture is stirred at room temperature for 1 hour. The precipitate which forms is removed by filtration and the filtrate is concentrated *in vacuo* to afford, as a white foam, methylsulfonylmethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate. That product has the structural formula



¹³C NMR (CDCl_3): δ 5.07 (s, 2, OCH_2SO_2), 2.97 (s, 3, SO_2CH_3).

Repetition of the procedure described in the preceding paragraph, but using only 1 mmol of *m*-chloroperoxybenzoic acid, affords methylsulfinylmethyl 17 α -ethoxycarbonyloxy-11 β -hydroxy-androst-4-en-3-one-17 β -carboxylate.

50 EXAMPLE 5A

• Substitution of an equivalent quantity of one of the starting materials listed below for the hydrocortisone used in Example 1 and substantial repetition of the procedure there detailed affords the indicated products:

| | Starting material | Product | |
|----|-------------------|---|----|
| 5 | fludrocortisone | 9 α -fluoro-11 β ,17 α -dihydroxy-androst-4-en-3-one-17 β -carboxylic acid, m.p. 250–253°C | 5 |
| 10 | betamethasone | 9 α -fluoro-11 β ,17 α -dihydroxy-16 β -methylandrosta-1,4-dien-3-one-17 β -carboxylic acid, m.p. 248–249°C | 10 |
| 15 | dexamethasone | 9 α -fluoro-11 β ,17 α -dihydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylic acid, m.p. 275–278.5°C | 15 |

20 EXAMPLE 5B 20

Substitution of an equivalent quantity of one of the starting materials listed below for the hydrocortisone used in Example 1 and substantial repetition of the procedure there detailed affords the indicated products:

| | Starting Material | Product | |
|----|---------------------|--|----|
| 25 | cortisone | 17 α -hydroxyandrost-4-en-3,11-dione-17 β -carboxylic acid | 25 |
| 30 | chloroprednisone | 6 α -chloro-17 α -hydroxyandrosta-1,4-dien-3,11-dione-17 β -carboxylic acid | 30 |
| 35 | flumethasone | 6 α , 9 α -difluoro-11 β , 17 α -dihydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylic acid | 35 |
| 40 | fluprednisolone | 6 α -fluoro-11 β ,17 α -dihydroxyandrosta-1,4-dien-3-one-17 β -carboxylic acid | 40 |
| 45 | meprednisone | 17 α -hydroxy-16 β -methylandrosta-1,4-dien-3,11-dione-17 β -carboxylic acid | 45 |
| 50 | methyl prednisolone | 11 β ,17 α -dihydroxy-6 α -methylandrosta-1,4-dien-3-one-17 β -carboxylic acid | 50 |
| 55 | paramethasone | 6 α -fluoro-11 β ,17 α -dihydroxy-16 α -Methylandrosta-1,4-dien-3-one-17 β -carboxylic acid | 55 |
| | prednisolone | 11 β ,17 α -dihydroxyandrosta-1,4-dien-3-one-17 β -carboxylic acid | |
| | prednisone | 17 α -hydroxyandrosta-1,4-dien-3,11-dione-17 β -carboxylic acid | |
| | triamcinolone | 9 α -fluoro-11 β ,16 α -,17 α -trihydroxyandrosta-1,4-dien-3-one-17 β -carboxylic acid | |

EXAMPLE 6A

Following the general procedure of Example 2 and substituting therein the appropriate reactants affords the following novel intermediates of the present invention:

| | | | | | | | | |
|----|---------------------|---|----------------------|----------------------|----------------------|----------|----------|-------------------------------------|
| 5 | | | | | | | 5 | |
| 10 | | | | | | | 10 | |
| 15 | | | | | | | 15 | |
| 20 | <u>Compound No.</u> | <u>R₃</u> | <u>R₃</u> | <u>R₄</u> | <u>R₅</u> | <u>Z</u> | <u>Δ</u> | <u>m.p.</u> |
| 25 | 6A-1 | CH ₂ C ₆ H ₅ | H | H | H | | 4 | 183-184°C (ethanol) |
| 30 | 6A-2 | C ₂ H ₅ | H | F | H | | 4 | 190-191°C (THF/hexane) |
| 35 | 6A-3 | C ₂ H ₅ | β-CH ₃ | F | H | | 1,4 | 128-129°C (THF/hexane) |
| 40 | 6A-4 | C ₂ H ₅ | α-CH ₃ | F | H | | 1,4 | 143-144.5°C (THF/hexane) |
| 45 | 6A-5 | iso-C ₃ H ₇ | α-CH ₃ | F | H | | 1,4 | 154.5-156°C (THF/hexane) |
| 50 | 6A-6 | iso-C ₄ H ₉ | H | H | H | | 4 | 125-126°C (THF/hexane) |
| 55 | 6A-7 | iso-C ₃ H ₇ | β-CH ₃ | F | H | | 1,4 | 171.5-172.5°C (THF/hexane) |
| 60 | 6A-8 | n-C ₃ H ₇ | H | H | H | | 4 | 156-157°C (THF/hexane) |
| | 6A-9 | n-C ₃ H ₇ | α-CH ₃ | F | H | | 1,4 | 157-158°C (THF/hexane) |
| | 6A-10 | | H | H | H | | 4 | 156-157.5°C (ether/hexane) |
| | 6A-11 | CH ₃ | α-CH ₃ | F | H | | 1,4 | 180-182°C (ethyl acetate) |
| | 6A-12 | n-C ₅ H ₁₁ | α-CH ₃ | F | H | | 1,4 | 138.5-139.5°C (THF/hexane) |
| | 6A-13 | C ₂ H ₅ | α-CH ₃ | F | F | | 1,4 | 157-158°C (decomp.) (THF/hexane) |
| | 6A-14 | C ₆ H ₅ | α-CH ₃ | F | H | | 1,4 | 246-248°C (THF/hexane) |
| | 6A-15 | CH ₂ CH ₂ Cl | α-CH ₃ | F | H | | 4 | 93-94°C (THF/hexane) |

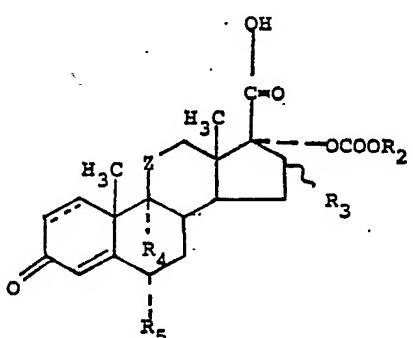
Compounds 6A-1 to 6A-15 above can be named as follows:

| | | |
|--------|---|----|
| 6A-1: | 17 α -benzyloxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylic acid | |
| 6A-2: | 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylic acid | |
| 6A-3: | 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 β -methylandrosta-1,4-dien-3-one- | |
| 5 | 17 β -carboxylic acid | 5 |
| 6A-4: | 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one- | |
| | 17 β -carboxylic acid | |
| 6A-5: | 9 α -fluoro-11 β -hydroxy-17 α -isopropoxycarbonyloxy-16 α -methylandrosta-1,4-dien-3- | |
| | one-17 β -carboxylic acid | |
| 10 | 11 β -hydroxy-17 α -isobutoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylic acid | 10 |
| 6A-7: | 9 α -fluoro-11 β -hydroxy-17 α -isopropoxycarbonyloxy-16 β -methylandrosta-1,4-dien-3- | |
| | one-17 β -carboxylic acid | |
| 6A-8: | 11 β -hydroxy-17 α -propoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylic acid | |
| 6A-9: | 9 α -fluoro-11 β -hydroxy-16 α -methyl-17 α -propoxycarbonyloxyandrosta-1,4-dien-3-one- | |
| 15 | 17 β -carboxylic acid | 15 |
| 6A-10: | 17 α -cyclohexyloxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylic acid | |
| 6A-11: | 9 α -fluoro-11 β -hydroxy-17 α -methoxycarbonyloxy-16 α -methylandrosta-1,4-dien-3-one- | |
| | 17 β -carboxylic acid | |
| 6A-12: | 17 α -n-pentyloxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3- | |
| 20 | one-17 β -carboxylic acid | 20 |
| 6A-13: | 17 α -ethoxycarbonyloxy-6 α -, 9 α -difluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3- | |
| | one-17 β -carboxylic acid | |
| 6A-14: | 17 α -phenoxy carbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one- | |
| | 17 β -carboxylic acid | |
| 25 | 6A-15: 17 α -(2-chloroethoxycarbonyloxy)-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylic acid | 25 |

EXAMPLE 6B

Following the general procedure of Example 2 and substituting therein the appropriate
30 reactants affords the following novel intermediates of the present invention: 30

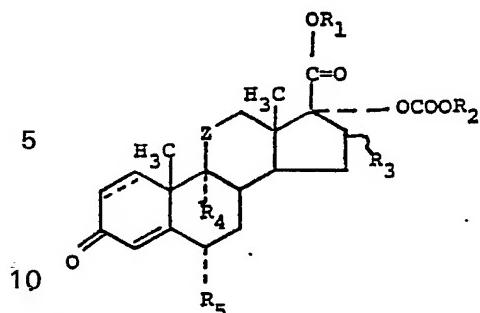
| | | | | | | | | |
|----|---------------------|----------------------------------|---------------------------|----------------|----------------|---|-----|----|
| | | | | | | | | |
| 5 | | | | | | | 5 | |
| | | | | | | | | |
| | | | | | | | | |
| 10 | | | | | | | 10 | |
| | | | | | | | | |
| | | | | | | | | |
| 15 | <u>Compound No.</u> | R ₂ | R ₃ | R ₄ | R ₅ | Z | A | 15 |
| | 6B-1 | C ₂ H ₅ | H | H | H | >C=O | 4 | |
| 20 | 6B-2 | CH ₃ | H | H | H | >C=O | 4 | 20 |
| | 6B-3 | CH ₃ | H | F | H |  | 4 | |
| 25 | 6B-4 | C ₂ H ₅ | α -CH ₃ | F | F |  | 1,4 | 25 |
| | 6B-5 | C ₂ H ₅ | H | H | F |  | 1,4 | |
| 30 | 6B-6 | C ₂ H ₅ | β -CH ₃ | H | H | >C=O | 1,4 | 30 |
| | 6B-7 | CH ₂ CCl ₃ | H | H | H |  | 4 | |
| 35 | 6B-8 | C ₂ H ₅ | α -CH ₃ | H | F |  | 1,4 | 35 |
| 40 | 6B-9 | C ₂ H ₅ | H | H | H |  | 1,4 | 40 |
| | 6B-10 | C ₂ H ₅ | H | H | H | >C=O | 1,4 | |



| | <u>Compound No.</u> | <u>R₂</u> | <u>R₃</u> | <u>R₄</u> | <u>R₅</u> | <u>Z</u> | <u>A</u> | |
|----|---------------------|---|-------------------------------------|----------------------|----------------------|---|----------|----|
| 5 | 6B-11 | C ₂ H ₅ | α-OCOOC ₂ H ₅ | F | H |  | 1,4 | 5 |
| 10 | 6B-12 | CH ₂ Cl | α-CH ₃ | F | H |  | 1,4 | 10 |
| 15 | 6B-13 | CH ₂ CH ₂ Cl | α-CH ₃ | F | H |  | 1,4 | 15 |
| 20 | 6B-14 | C ₂ H ₅ | H | H | Cl |  | 1,4 | 20 |
| 25 | 6B-15 | C ₆ H ₅ | H | H | H |  | 4 | 25 |
| 30 | 6B-16 |  | H | H | H |  | 4 | 30 |
| 35 | 6B-17 |  | H | H | H |  | 4 | 35 |
| 40 | 6B-18 | CH=CH ₂ | H | H | H |  | 4 | 40 |
| 45 | 6B-19 | CH ₂ OCH ₃ | H | H | H |  | 4 | 45 |
| | 6B-20 | CH ₂ SCH ₃ | H | H | H |  | 4 | |
| | 6B-21 | CH ₂ CH ₂ NHCOCH ₃ | H | H | H |  | 4 | |
| | 6B-22 | CH ₂ CH ₂ OCOCH ₃ | H | H | H |  | 4 | |
| | 6B-23 | C ₂ H ₅ | H | H | CH ₃ |  | 1,4 | |
| | 6B-24 | CH ₂ SO ₂ CH ₃ * | H | H | H |  | 4 | |
| | 6B-25 | CH ₂ SOCH ₃ * | H | H | H |  | 4 | |

*prepared from 6B-20 by subsequent reaction with *m*-chloroperbenzoic acid.

EXAMPLE 7A
 50 Following the general procedure of Example 3 and substituting therein the appropriate reactants affords the following compounds:



| Compound No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | Z | Δ | m.p. |
|--------------|----------------|--|--|-------------------|----------------|---|---|--------------------------------------|
| 15 | 7A-1 | CH ₂ Cl | C ₂ H ₅ | H | F | H |  | 4 228-229°C (THF/hexane) |
| 20 | 7A-2 | CH ₂ Cl | C ₂ H ₅ | β-CH ₃ | F | H |  | 1,4 220-221°C (THF/hexane) |
| 25 | 7A-3 | CH ₂ Cl | C ₂ H ₅ | α-CH ₃ | F | H |  | 1,4 230-235°C (THF/hexane) |
| 30 | 7A-4 | CH ₂ Cl | C ₂ H ₅ | H | H | H |  | 1,4 220.5-223.5°C (THF/hexane) |
| 35 | 7A-5 | CH ₂ Cl | iso-C ₃ H ₇ | H | H | H |  | 1,4 197-198°C (THF/hexane) |
| 40 | 7A-6 | CH ₂ Cl | C ₂ H ₅ | H | F | H |  | 1,4 245-248°C (THF/hexane) |
| 45 | 7A-7 | CH ₂ Cl | iso-C ₃ H ₇ | α-CH ₃ | F | H |  | 1,4 184.5-186°C (THF/hexane) |
| 50 | 7A-8 | CH ₂ Cl | iso-C ₃ H ₇ | β-CH ₃ | F | H |  | 1,4 174-175.5°C (THF) |
| 55 | 7A-9 | CH ₂ Cl | iso-C ₄ H ₉ | H | H | H |  | 4 140-141°C (THF/isopropyl ether) |
| 60 | 7A-10 | CH ₂ Cl | -C ₆ H ₅ | H | H | H |  | 4 148-150°C (isopropyl ether hexane) |
| 65 | 7A-11 | CH ₂ Cl | n-C ₃ H ₇ | H | H | H |  | 4 181-182°C (THF/hexane) |
| 70 | 7A-12 | CH ₂ Cl | n-C ₃ H ₇ | α-CH ₃ | F | H |  | 1,4 176-176.5°C (THF/hexane) |
| 75 | 7A-13 | CH ₃ | iso-C ₃ H ₇ | H | H | H |  | 4 211.5-213.5°C (THF/hexane) |
| 80 | 7A-14 | CH ₂ OC ₂ H ₅ | iso-C ₃ H ₇ | H | H | H |  | 4 137-138°C (THF/hexane) |
| 85 | 7A-15 | CH ₂ Cl | CH ₂ -C ₆ H ₅ | H | H | H |  | 4 182-183°C (ethanol) |

| Compound No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | Z | Δ | m.p. | |
|--------------|--------------------------------|--|------------------------------|--------------------------------------|----------------|---|--|------------------------------|--|
| 5 | CH_3 CHCl | iso- C_3H_7 | H | H | H |  | 4 | 181-182.5°C (THF/hexane) | |
| | CH_3 CHCl | iso- C_3H_7 | H | H | H |  | 4 | 199-200°C (THF/hexane) | |
| 10 | 7A-17 | $\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$ | iso- C_3H_7 | H | H |  | 4 | 73-74°C (isopropyl ether) | |
| 15 | CH_3 CHCl | iso- C_3H_7 | $\beta\text{-CH}_3$ | F | H |  | 1,4 | 167.5-169°C (THF/hexane) | |
| | CH_3 CHCl | iso- C_3H_7 | $\beta\text{-CH}_3$ | F | H |  | 1,4 | 163-164°C (THF/hexane) | |
| 20 | 7A-19 | CH_2Cl | iso- C_3H_7 | $\beta\text{-CH}_3$ | F | H |  | 1,4 | 200-201°C (THF/isopropyl ether) |
| 25 | 7A-20 | CH_2Cl | C_2H_5 | $\alpha\text{-CH}_3$ | F | H |  | 1,4 | 138-140°C (THF/isopropyl ether) |
| 30 | 7A-21 | CH_2Cl | CH_3 | $\alpha\text{-CH}_3$ | F | H |  | 1,4 | 260-263°C (THF/hexane) |
| 35 | 7A-22 | CH_2F | iso- C_3H_7 | H | H | H |  | 4 | 207.5-210°C (THF/hexane) |
| 40 | 7A-23 | CH_2Cl | n- C_5H_{11} | $\alpha\text{-CH}_3$ | F | H |  | 1,4 | 176-177°C (THF/hexane) |
| 45 | 7A-24 | CH_2Cl | C_2H_5 | $\alpha\text{-OC(=O)OC}_2\text{H}_5$ | H | F |  | 1,4 | 153-154°C (THF/hexane) |
| 50 | 7A-25 | CH_2F | C_2H_5 | $\alpha\text{-CH}_3$ | F | H |  | 1,4 | 239-240.5°C (THF/hexane) |
| 55 | 7A-26 | CH_2COOC_3 | C_2H_5 | H | H | H |  | 4 | NMR (CDCl_3) 65.76 (s, 2, OCH_2O), 2.01 (s, 3, OOCCH_3) |

* diastereomers

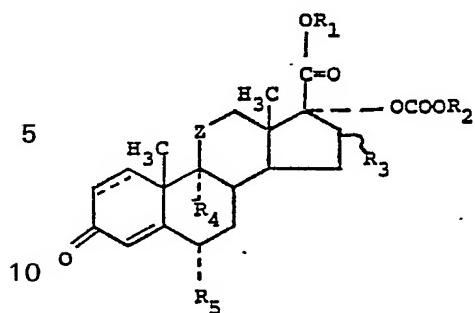
| Compound No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | Z | Δ | m.p. |
|--------------|----------------|------------------------------------|-----------------------------------|-------------------|----------------|---|---|--------------------------------------|
| 45 | 7A-27 | CH ₂ Cl | C ₂ H ₅ | α-CH ₃ | F | F |  | 1,4 195-197°C (THF/hexane) |
| 50 | 7A-28 | CH ₂ CH ₂ Cl | C ₂ H ₅ | α-CH ₃ | F | H |  | 1,4 243-245°C (THF/hexane) |
| 55 | 7A-29 | CH ₃ | C ₂ H ₅ | α-CH ₃ | F | H |  | 1,4 258.5-262.5°C (THF/hexane) |
| | 7A-30 | CH ₂ CH ₂ Cl | iso-C ₃ H ₇ | H | H | H |  | 4 188.5-189.5°C (THF/hexane) |

The foregoing compounds can be named as follows:

| | | |
|-----------|---|----|
| 7A-1: | chloromethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate | |
| 5 7A-2: | chloromethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 β -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 5 |
| 7A-3: | chloromethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate | |
| 7A-4: | chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxy-androsta-1,4-dien-3-one-17 β -carboxylate | |
| 10 7A-5: | chloromethyl 11 β -hydroxy-17 α -isopropoxycarbonyloxy-androsta-1,4-dien-3-one-17 β -carboxylate | 10 |
| 7A-6: | chloromethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxyandrosta-1,4-dien-3-one-17 β -carboxylate | |
| 15 7A-7: | chloromethyl 9 α -fluoro-11 β -hydroxy-17 α -isopropoxycarbonyloxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 15 |
| 7A-8: | chloromethyl 9 α -fluoro-11 β -hydroxy-17 α -isopropoxycarbonyloxy-16 β -methylandrosta-1,4-dien-3-one-17 β -carboxylate | |
| 7A-9: | chloromethyl 11 β -hydroxy-17 α -isobutoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylate | |
| 20 7A-10: | chloromethyl 17 α -cyclohexyloxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate | 20 |
| 7A-11: | chloromethyl 11 β -hydroxy-17 α -propoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylate | |
| 25 7A-12: | chloromethyl 9 α -fluoro-11 β -hydroxy-16 α -methyl-17 α -propoxycarbonyloxyandrosta-1,4-dien-3-one-17 β -carboxylate | 25 |
| 7A-13: | methyl 11 β -hydroxy-17 α -isopropoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylate | |
| 7A-14: | ethoxymethyl 11 β -hydroxy-17 α -isopropoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylate | |
| 30 7A-15: | chloromethyl 17 α -benzyloxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate | 30 |
| 7A-16: | 1-chloroethyl 11 β -hydroxy-17 α -isopropoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylate | |
| 7A-17: | ethoxycarbonylmethyl 11 β -hydroxy-17 α -isopropoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylate | |
| 35 7A-18: | 1-chloroethyl 9 α -fluoro-11 β -hydroxy-17 α -isopropoxycarbonyloxy-16 β -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 35 |
| 7A-19: | chloromethyl 9 α -fluoro-17 α -isopropoxycarbonyloxy-16 β -methylandrosta-1,4-dien-3,11-dione-17-carboxylate | |
| 40 7A-20: | chloromethyl 9 α -fluoro-17 α -isopropoxycarbonyloxy-16 α -methylandrosta-1,4-dien-3,11-dione-17-carboxylate | 40 |
| 7A-21: | chloromethyl 9 α -fluoro-11 β -hydroxy-17 α -methoxycarbonyloxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate | |
| 7A-22: | fluoromethyl 11 β -hydroxy-17 α -isopropoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylate | |
| 45 7A-23: | chloromethyl 9 α -fluoro-11 β -hydroxy-16 α -methyl-17 α -pentyloxycarbonyloxyandrosta-1,4-dien-3-one-17 β -carboxylate | 45 |
| 7A-24: | chloromethyl 16 α ,17 α -di(ethoxycarbonyloxy)-6 α -fluoro-11 β -hydroxyandrosta-1,4-dien-3-one-17 β -carboxylate | |
| 50 7A-25: | fluoromethyl 17 α -ethoxycarbonyloxy-9 α -flouro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 50 |
| 7A-26: | acetoxyethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate | |
| 7A-27: | chloromethyl 17 α -ethoxycarbonyloxy-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate | |
| 55 7A-28: | 2-chloroethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate | 55 |
| 7A-29: | methyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate | |
| 60 7A-30: | 2-chloroethyl 17 α -isopropoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate | 60 |

EXAMPLE 7B

Following the general procedure of Examples 3 or 4 and substituting therein the appropriate reactants affords the following compounds:



| Compound No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | Z | Δ | |
|--------------|----------------|--|---|----------------|----------------|---|---|---|
| 15 | 7B-1 | C ₂ H ₅ | C ₂ H ₅ | H | H | H |  | 4 |
| 20 | 7B-2 | C ₄ H ₉ | CH ₂ C ₆ H ₅ | H | H | H |  | 4 |
| 25 | 7B-3 | CH ₂ COOC ₂ H ₅ | C ₂ H ₅ | H | H | H |  | 4 |
| 30 | 7B-4 | CH ₂ COOCH ₃ | C ₂ H ₅ | H | H | H |  | 4 |
| 35 | 7B-5 | CH ₂ Cl | C ₆ H ₅ | H | H | H |  | 4 |
| 40 | 7B-6 | CH ₂ Cl |  | H | H | H |  | 4 |
| 45 | 7B-7 | CH ₂ Cl | CH ₂ SCH ₃ | H | H | H |  | 4 |
| 50 | 7B-8 | C ₄ H ₉ | C ₂ H ₅ | H | H | H | >C = O | 4 |
| | 7B-9 | CH ₂ Cl | CH ₃ | H | H | H | >C = O | 4 |
| | 7B-10 | CH ₂ Cl | C ₂ H ₅ | H | H | H | >C = O | 4 |
| | 7B-11 | CH ₂ SCH ₃ | C ₂ H ₅ | H | H | H | >C = O | 4 |
| | 7B-12 | CH ₂ SO ₂ CH ₃ | C ₂ H ₅ | H | H | H | >C = O | 4 |
| | 7B-13 | CH ₂ SOCH ₃ | C ₂ H ₅ | H | H | H | >C = O | 4 |
| | 7B-14 | CH ₂ Cl | CH ₃ | H | F | H |  | 4 |
| | 7B-15 | CH ₂ SCH ₃ | C ₂ H ₅ | H | F | H |  | 4 |

| Compound No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | Z | Δ | |
|--------------|---|---|-------------------------------|-------------------|----------------|---------------------|---------------------|-----|
| 7B-16 | CH ₂ SO ₂ CH ₃ | C ₂ H ₅ | H | F | H | >C< OH H | 4 | |
| 5 | 7B-17 | CH ₂ SCH ₃ | C ₂ H ₅ | β-CH ₃ | F | H | >C< OH H | 1,4 |
| 10 | 7B-18 | CH ₂ SO ₂ CH ₃ | C ₂ H ₅ | β-CH ₃ | F | H | >C< OH H | 1,4 |
| 15 | 7B-19 | CH ₂ Cl | C ₂ H ₅ | H | H | Cl | >C=O | 1,4 |
| 20 | 7B-20 | CH ₂ SCH ₃ | C ₂ H ₅ | H | H | Cl | >C=O | 1,4 |
| 25 | 7B-21 | CH ₂ SO ₂ CH ₃ | C ₂ H ₅ | H | H | Cl | >C=O | 1,4 |
| 30 | 7B-22 | CH ₂ SCH ₃ | C ₂ H ₅ | α-CH ₃ | F | H | >C< OH H | 1,4 |
| 35 | 7B-23 | CH ₂ SO ₂ CH ₃ | C ₂ H ₅ | α-CH ₃ | F | H | >C< OH H | 1,4 |
| 40 | 7B-24 | CH ₂ Cl | C ₂ H ₅ | α-CH ₃ | F | F | >C< OH H | 1,4 |
| | 7B-25 | CH ₂ SCH ₃ | C ₂ H ₅ | α-CH ₃ | F | F | >C< OH H | 1,4 |
| | 7B-26 | CH ₂ SO ₂ CH ₃ | C ₂ H ₅ | α-CH ₃ | F | F | >C< OH H | 1,4 |
| | 7B-27 | CH ₂ Cl | C ₂ H ₅ | H | H | F | >C< OH H | 1,4 |
| | 7B-28 | CH ₂ SCH ₃ | C ₂ H ₅ | H | H | F | >C< OH H | 1,4 |
| | 7B-29 | CH ₂ SO ₂ CH ₃ | C ₂ H ₅ | H | H | F | >C< OH H | 1,4 |
| | 7B-30 | CH ₂ Cl | C ₂ H ₅ | β-CH ₃ | H | H | >C=O | 1,4 |
| | 7B-31 | CH ₂ SCH ₃ | C ₂ H ₅ | β-CH ₃ | H | H | >C=O | 1,4 |
| | 7B-32 | CH ₂ SO ₂ CH ₃ | C ₂ H ₅ | β-CH ₃ | H | H | >C=O | 1,4 |

| Compound No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | Z | Δ | |
|--------------|--|---|--------------------------------------|----------------|-----------------|-------------------------|-----|----|
| 5 | 7B-33 CH ₂ Cl | C ₂ H ₅ | H | H | CH ₃ | >C _— OH H | 1,4 | 5 |
| | 7B-34 CH ₂ SCH ₃ | C ₂ H ₅ | H | H | CH ₃ | >C _— OH H | 1,4 | |
| 10 | 7B-35 CH ₂ SO ₂ CH ₃ | C ₂ H ₅ | H | H | CH ₃ | >C _— OH H | 1,4 | 10 |
| | 7B-36 CH ₂ Cl | C ₂ H ₅ | α-CH ₃ | H | F | >C _— OH H | 1,4 | |
| 15 | 7B-37 CH ₂ SCH ₃ | C ₂ H ₅ | α-CH ₃ | H | F | >C _— OH H | 1,4 | 15 |
| | 7B-38 CH ₂ SO ₂ CH ₃ | C ₂ H ₅ | α-CH ₃ | H | F | >C _— OH H | 1,4 | |
| 20 | 7B-39 CH ₂ SCH ₃ | C ₂ H ₅ | H | H | H | >C _— OH H | 1,4 | 20 |
| | 7B-40 CH ₂ SO ₂ CH ₃ | C ₂ H ₅ | H | H | H | >C _— OH H | 1,4 | |
| 25 | 7B-41 CH ₂ Cl | C ₂ H ₅ | H | H | H | >C = O | 1,4 | 25 |
| | 7B-42 CH ₂ SCH ₃ | C ₂ H ₅ | H | H | H | >C = O | 1,4 | |
| 30 | 7B-43 CH ₂ SO ₂ CH ₃ | C ₂ H ₅ | H | H | H | >C = O | 1,4 | 30 |
| | 7B-44 CH ₂ Cl | C ₂ H ₅ | α-OCOOCH ₂ H ₅ | F | H | >C _— OH H | 1,4 | |
| 35 | 7B-45 CH ₂ SCH ₃ | C ₂ H ₅ | α-OCOOCH ₂ H ₅ | F | H | >C _— OH H | 1,4 | 35 |
| | 7B-46 CH ₂ SO ₂ CH ₃ | C ₂ H ₅ | α-OCOOCH ₂ H ₅ | F | H | >C _— OH H | 1,4 | |
| 40 | 7B-47 CH ₂ Cl | C ₂ H ₅ | α-OH | H | F | >C _— OH H | 1,4 | 40 |
| | 7B-48 CH ₂ Cl | -  | α-CH ₃ | F | H | >C _— OH H | 1,4 | |
| | 7B-49 CH ₂ Cl | CH ₂ CH ₂ Cl | α-CH ₃ | F | H | >C _— OH H | 1,4 | |
| | 7B-50 CH ₃ | CH ₂ Cl | α-CH ₃ | F | H | >C _— OH H | 1,4 | |

| Compound No. | R ₁ | R ₂ | R ₃ | R ₄ | R ₅ | Z | Δ | |
|--------------|-------------------------------|--|--|----------------|----------------|----------------|----------------|----|
| 7B-51 | C ₄ H ₉ | CH ₂ CCl ₃ | H | H | H | >C< H OH | 4 | |
| 5 | 7B-52 | CH ₂ CON(C ₂ H ₅) ₂ | C ₂ H ₅ | H | H | H | >C< H OH | 4 |
| 10 | 7B-53 | CH ₂ CON(ether) | CH ₃ | H | H | H | >C< H OH | 4 |
| 15 | 7B-54 | C ₆ H ₅ | C ₂ H ₅ | H | H | H | >C< H OH | 4 |
| 20 | 7B-55 | CH ₂ C ₆ H ₅ | CH ₃ | H | H | H | >C< H OH | 4 |
| 25 | 7B-56 | CH ₂ S | C ₂ H ₅ | H | H | H | >C< H OH | 4 |
| 30 | 7B-57 | CH ₂ Cl | cyclohexyl | H | H | H | >C< H OH | 4 |
| 35 | 7B-58 | CH ₂ Cl | CH=CH ₂ | H | H | H | >C< H OH | 4 |
| 40 | 7B-59 | CH ₂ Cl | CH ₂ OCH ₃ | H | H | H | >C< H OH | 4 |
| 45 | 7B-60 | CH ₂ Cl | CH ₂ CH ₂ NHOOCCH ₃ | H | H | H | >C< H OH | 4 |
| 50 | 7B-61 | CH ₂ Cl | CH ₂ CH ₂ COOCH ₃ | H | H | H | >C< H OH | 4 |
| | 7B-62 | CH ₂ CON(ether) | C ₂ H ₅ | H | H | H | >C< H OH | 4 |
| | | | | | | | | 40 |
| | | | | | | | | 45 |
| | | | | | | | | 50 |

55 *prepared from Example 6B-24 and 6B-25 respectively by reaction with ClCH₂I, or from Example 7B-7 by reaction with *m*-chloroperbenzoic acid. 55

EXAMPLE 8

An equivalent quantity of 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylic acid is substituted for the 11 β -hydroxy-17 α -methoxycarbonyloxyandrost-4-en-3-one-17 β -carboxylic acid starting material employed in Example 3, and the procedure of the first paragraph of that example is substantially repeated. There are thus obtained, as the intermediate salt, sodium 11 β , 17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate, and, as the final product, chloromethyl 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate, melting at 184-186°C (recrystallization from tetrahydrofuran-etherhexane). 60 65

EXAMPLE 9

An equivalent quantity of $11\beta,17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylic acid is substituted for the 17α -ethoxycarbonyloxy- 11β -hydroxyandrost-4-en-3-one- 17β -carboxylic acid starting material employed in Example 4, and the procedure of the first paragraph of that example is

5 substantially repeated. There are thus obtained, as the intermediate salt, sodium $11\beta,17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylate, and as the final product, methylthiomethyl $11\beta,17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylate. 5

Substitution of an equivalent quantity of methylthiomethyl $11\beta,17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylate for the methylthiomethyl 17α -ethoxycarbonyloxy- 11β -hydroxyandrost-4-en-10 3-one- 17β -carboxylate used in the second paragraph of Example 4 and substantial repetition of the procedure there detailed affords methylsulfonylmethyl $11\beta,17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylate. 10

EXAMPLE 10A

15 The procedure of each paragraph of Example 2 is substantially repeated, substituting an equivalent quantity of each of the following starting materials for the steroids employed therein: chloromethyl $11\beta,17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylate; and methylthiomethyl $11\beta,17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylate. The following soft anti-inflammatory agents of formula (I) are obtained: 15

20



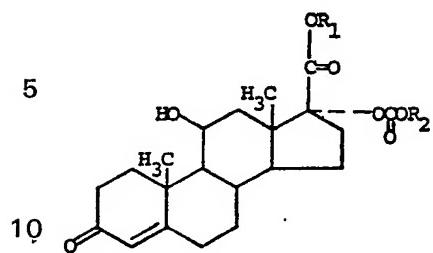
| | Compound No. | R ₁ | R ₂ | m.p. | |
|----|--------------|----------------------------------|-----------------------------------|---------------------------------|----|
| 35 | 10A-1 | CH ₂ Cl | CH ₃ | 171–173°C | 35 |
| | 10A-2 | CH ₂ Cl | C ₂ H ₅ | 197–200°C (THF/hexane) | |
| | 10A-3 | CH ₂ SCH ₃ | C ₂ H ₅ | 137.5–138°C (ether/hexane) | |
| 40 | 10A-4 | CH ₂ Cl | C ₄ H ₉ | 99.5–102°C (THF/hexane) | 40 |
| | 10A-5 | CH ₂ Cl | iso-C ₃ H ₇ | 183.5–184.5°C (THF/hexane) | |
| | 10A-6* | CH ₂ Cl | iso-C ₄ H ₉ | 140–141°C (THF/isopropyl ether) | |

*utilizing isobutyl chloroformate as the alkyl chloroformate reactant

45

EXAMPLE 10B

The procedure of each paragraph of Example 2 is substantially repeated, substituting an equivalent quantity of each of the following starting materials for the steroids employed therein: 50 methylthiomethyl $11\beta,17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylate; and methylsulfonylmethyl $11\beta,17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylate. The following soft anti-inflammatory agents of formula (I) are obtained.

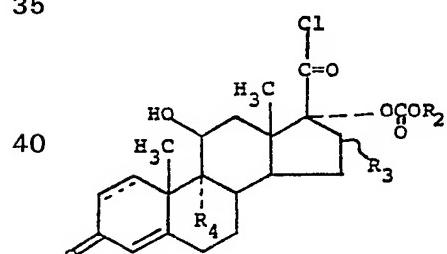


| 15 | Compound No. | R ₁ | R ₂ |
|----|--------------|---|---------------------------------|
| 20 | 10B-1 | CH ₃ SCH ₃ | CH ₃ |
| | 10B-2 | CH ₂ SCH ₃ | C ₄ H ₉ |
| | 10B-3 | CH ₂ SCH ₃ | i-C ₃ H ₇ |
| | 10B-4 | CH ₂ SO ₂ CH ₃ | CH ₃ |
| | 10B-5 | CH ₂ SO ₂ CH ₃ | C ₂ H ₅ |
| | 10B-6 | CH ₂ SO ₂ CH ₃ | C ₄ H ₉ |
| | 10B-7 | CH ₂ SO ₂ CH ₃ | i-C ₃ H ₇ |

Other representative species, e.g. compounds of Examples 7A and 7B, can likewise be prepared according to the procedures of Examples 8 through 10.

30 EXAMPLE 11

EXAMPLE 11 The products of Example 2 and Example 6A–4 are each allowed to react, first with diethylchlorophosphate and then with CH_3SNa in chloroform for approximately 6 hours. The following intermediates are obtained in the first step:



| | R ₂ | R ₃ | R ₄ | Δ |
|----|---------------------------------|-------------------|----------------|-----|
| 50 | CH ₃ | H | H | 4 |
| | C ₂ H ₅ | H | H | 4 |
| | C ₄ H ₉ | H | H | 4 |
| | i-C ₃ H ₇ | H | H | 4 |
| 55 | C ₂ H ₅ | α-CH ₃ | F | 1,4 |

and the following compounds of formula (I) are obtained in the second step:

| | | | | |
|----|---------------------------------|-------------------|----------------|-----|
| | | | | |
| 5 | | | | 5 |
| | | | | |
| 10 | | | | 10 |
| | | | | |
| 15 | | | | 15 |
| | R ₂ | R ₃ | R ₄ | Δ |
| 20 | CH ₃ | H | H | 4 |
| | C ₂ H ₅ | H | H | 4 |
| | C ₄ H ₉ | H | H | 4 |
| | i-C ₃ H ₇ | H | H | 4 |
| | C ₂ H ₅ | α-CH ₃ | F | 1,4 |

25 When the remaining products of Example 6A and those of Example 6B are treated according to the above procedure, the corresponding compounds of the formula 25

| | | | | |
|----|--|--|--|----|
| | | | | |
| 30 | | | | 30 |
| | | | | |
| 35 | | | | 35 |
| | | | | |
| 40 | | | | 40 |

wherein the various structural parameters represented by R₂, R₃, R₄, R₅, Z and the dotted line are identical to those of compounds 6A1–6A3, 6A5–6A11, and 6B1–6B25 of Examples 6A 45 and 6B are obtained. 45

EXAMPLE 12

Chloromethyl 11β,17α-dihydroxyandrost-4-en-3-one-17β-carboxylate (0.01 mol) is dissolved in toluene (100 milliliters) and the solution is cooled to approximately 0°C. Phosgene is then 50 bubbled into the solution, while maintaining the reaction mixture at low temperature, until the reaction is complete (approximately 2 hours). The solvent and excess phosgene are removed by evaporation to leave the crude 17α-chlorocarbonyloxy compound of the formula 50

| | | | | |
|----|--|--|--|----|
| | | | | |
| 55 | | | | 55 |
| | | | | |
| 60 | | | | 60 |

The intermediate (0.01 mol) obtained above is then combined with ethanol (0.02 mol) containing 2,6-dimethylpyridine (0.01 mol) and allowed to react at room temperature for 6 hours. At the end of that time, the desired chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate is isolated from the reaction mixture. The compound melts at 5 197–200°C, after crystallization.

Substitution of an equivalent quantity of methylthiomethyl 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate for the chloromethyl 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate used above and substantial repetition of the foregoing procedure affords methylthiomethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate, melting at 133–136°C, after 10 crystallization. That compound can then, if desired, be converted to the corresponding sulfonyl or sulfinyl compounds as described in Example 4.

Other representative species, e.g., the compounds of Example 3, paragraphs 1, 3, 4 and 5, and the compounds of Examples 7A and 7B can be prepared in like manner from reaction of the corresponding 17 α -hydroxy 17 β -carboxylates with the appropriate alcohols, including, when 15 appropriate, subsequent treatment with *m*-chloroperoxybenzoic acid as in Example 4.

EXAMPLE 13

The procedure of the first paragraph of Example 12 is repeated, except that an equivalent quantity of 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylic acid is used in place of the 20 chloromethyl 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate. The crude intermediate thus obtained has the formula 20



That intermediate is then subjected to the procedure of the second paragraph of Example 12, to afford 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylic acid, identical to the product of Example 2, paragraph 2.

The other compounds of Examples 2, 6A and 6B can be prepared using the same general 40 procedure. 40

EXAMPLE 14

Chloromethyl 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate (0.02 mol) is combined with diethylcarbonate (0.2 mol) containing 20 mg of *p*-toluenesulfonic acid. The reaction 45 mixture is maintained at room temperature for 4 hours, then heated to about 80 to 85°C; the remaining ethanol which forms is removed by distillation under reduced pressure. Obtained as the residue is crude chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate, melting at 197–200°C, after crystallization. 45

Substitution of an equivalent quantity of methylthiomethyl 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate for the chloromethyl 11 β ,17 α -dihydroxyandrost-4-en-3-one-17 β -carboxylate used above and substantial repetition of the foregoing procedure affords methylthiomethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate, melting at 133–136°C. 50

That compound can then, if desired, be converted to the corresponding sulfonyl or sulfinyl compound as described in Example 4.

Other representative species, e.g., the compounds of Example 3, paragraphs 1, 3, 4 and 5, and the compounds of Examples 7A and 7B, can be prepared in like manner from reaction of the corresponding 17 α -hydroxy-17 β -carboxylates with the appropriate carbonates of the 55

type R_2OCOR_2 (including, when appropriate, subsequent 60

treatment with *m*-chloroperoxybenzoic acid as in Example 4).

EXAMPLE 15

To a solution of 8.7 grams of $11\beta, 17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylic acid and 9.6 milliliters of triethylamine in 100 milliliters of dry dichloromethane, is added 10 grams of ethyl chloroformate, dropwise at 0 to 5°C. The reaction mixture is gradually allowed to warm to room temperature and the insoluble material is removed by filtration. The filtrate is washed successively with 3% aqueous sodium bicarbonate, 1% hydrochloric acid, and water, then is dried over anhydrous magnesium sulfate. The solvent is concentrated under reduced pressure and the residue is crystallized to give 10.5 grams of ethoxycarbonyl 17α -ethoxycarbonyloxy- 11β -hydroxyandrost-4-en-3-one- 17β -carboxylate, melting at 158–159°C.

10

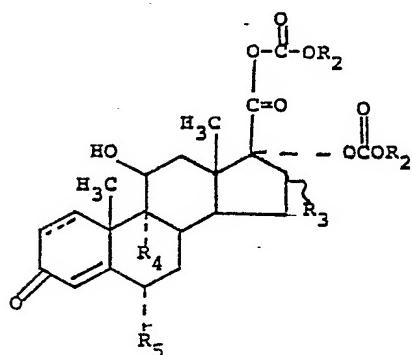
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EXAMPLE 16

Following the general method described in Example 15 and substituting therein the appropriate reactants affords the following additional compounds:

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15



30

30

| Compound No. | R ₂ | R ₃ | R ₄ | R ₅ | Δ | melting point |
|--------------|--|----------------|----------------|----------------|---|---------------------------------|
| 35 16-A | -CH ₂ CH ₃ | H | F | H | 4 | 110–111°C (THF-isopropyl ether) |
| 16-B | iso-C ₃ H ₇ | H | H | H | 4 | 200–203°C |
| 16-C | -CH ₂ CH ₂ CH ₃ | H | H | H | 4 | 142–143°C (THF) |

40

40

EXAMPLE 17

To a solution of 9.8 grams of ethoxycarbonyl 17α -ethoxycarbonyloxy- 11β -hydroxyandrost-4-en-3-one- 17β -carboxylate in 100 milliliters of tetrahydrofuran and 120 milliliters of ethanol are added 42 milliliters of 5% aqueous sodium bicarbonate. The mixture is stirred at room temperature for about 30 hours and adjusted to pH 2 to 3 by adding 1N hydrochloric acid. The insoluble material is isolated by filtration. Recrystallization from a mixture of tetrahydrofuran and n-hexane gives 6 grams of 17α -ethoxycarbonyloxy- 11β -hydroxyandrost-4-en-3-one- 17β -carboxylic acid having a melting point of 192–195°C.

50

45

The compound obtained in Example 2, first paragraph, and the compounds of Example 6A can be prepared, following the same procedure as above and substituting therein appropriate reactants.

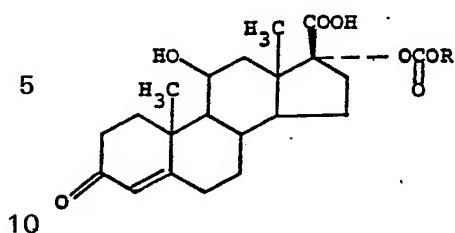
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EXAMPLE 18

55

55

Following the general method described in Example 17 and substituting therein the appropriate reactants affords the following compounds:



| Compound No. | R | melting point | |
|--------------|--|----------------------------|----|
| 15 | | | 15 |
| 18-A | $ \begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}- \\ \\ \text{CH}_3 \end{array} $ | 144.5–146.5°C (THF/hexane) | |
| 20 | | | 20 |
| 18-B | $-(\text{CH}_2)_3\text{CH}_3$ | 164–166°C (THF/hexane) | |

EXAMPLE 19

EXAMPLE 15

To a solution of 8.7 grams of $11\beta,17\alpha$ -dihydroxyandrost-4-en-3-one- 17β -carboxylic acid and 10 grams of triethylamine in 100 milliliters of dichloromethane, a solution of 13.2 grams of n-propyl chloroformate in 200 milliliters of dichloromethane is added dropwise over 1–1.5 hours with ice-cooling. The reaction mixture is allowed to warm to room temperature over a 2 hour period, then is washed successively with 3% aqueous sodium bicarbonate, 1N hydrochloric acid, and water and dried over anhydrous sodium sulfate. The solvent is concentrated under reduced pressure. Crystallization from a mixture of ether and n-hexane gives 10.5 grams of propoxycarbonyl 11β -hydroxy- 17α -propoxycarbonyloxyandrost-4-en-3-one- 17β -carboxylate, which is dissolved in 40 milliliters of pyridine. To that solution, 300 milliliters of water are added dropwise over a 1 to 1.5 hour period. The mixture is stirred for one hour and adjusted to pH 2 to 2.5 by adding concentrated hydrochloric acid with ice-cooling. The mixture is then extracted with chloroform, washed successively with 1N hydrochloric acid and water, and then dried over sodium sulfate. The solvent is concentrated under reduced pressure, and the residue is recrystallized from a mixture of acetone and tetrahydrafuran to give 7.7 grams of 11β -hydroxy- 17α -propoxycarbonyloxyandrost-4-en-3-one- 17β -carboxylic acid, melting at 156–157°C.

EXAMPLE 20

45 Following the general procedure detailed in Example 19, but utilizing the appropriate starting materials and reaction conditions, affords the remaining compounds of Example 6A. 45

EXAMPLE 21

EXAMPLE 21 Chloromethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate (2 grams) is dissolved in anhydrous dichloromethane (200 milliliters) and pyridinium chlorochromate (3.5 grams) is added at room temperature, with stirring. The resultant mixture is stirred for 24 hours, then the solvent is concentrated under reduced pressure at about 10 to 20°C. The residue is subjected to column chromatography on silica gel (Kiesel gel 60), using chloroform as an eluting solvent, followed by recrystallization from a mixture of tetrahydrofuran and isopropyl ether to give chloromethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-16 α -methylandrosta-1,4-dien-3,11-dione-17 β -carboxylate, in the yield of 1.7 grams, melting at 138–140°C.

EXAMPLE 22

60 By a method similar to that described in Example 21, there is obtained chloromethyl 9 α -fluoro-17 α -isopropoxycarbonyloxy-16 β -methylandrosta-1,4-dien-3,11-dione-17 β -carboxylate, melting at 200–201°C.

EXAMPLE 23

Utilizing the general procedure of Example 3, but substituting the appropriate reactants therein, affords methyl 17 α -(2-chloroethoxy)carbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate. That product, after recrystallization from isopropanol,

5 melts at 223-227°C.

5

EXAMPLE 24

In the same general manner as in Example 3, there is obtained 2-chloroethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate.

10 That product, after recrystallization from tetrahydrofuran-hexane, melts at 243-245°C.

10

EXAMPLE 25

Chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate (0.01 mol) and 1,2-dimethylpyrrolidine (0.01 mol) are dissolved in acetonitrile (80 milliliters), and
15 heated to the reflux temperature. The reaction mixture is maintained at that temperature, with stirring, for approximately 4 hours. About 65 ml of acetonitrile are removed; then, the mixture is cooled to room temperature and excess ethyl ether is added to cause precipitation. The precipitate is separated by filtration, washed, and dried *in vacuo*, thus affording the desired quaternary ammonium salt of the formula

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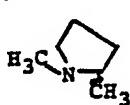
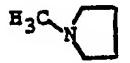
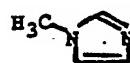
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| <u>R₂</u> | <u>N ≡</u> | |
|------------------------------------|---|----|
| 5 CH ₃ |  | 5 |
| 10 i-C ₃ H ₇ | N(C ₂ H ₅) ₃ | 10 |
| 10 C ₄ H ₉ |  | |
| 15 C ₂ H ₅ |  | 15 |
| 20 C ₂ H ₅ |  | 20 |
| 25 C ₂ H ₅ | N(C ₂ H ₅) ₃ | 25 |
| C ₂ H ₅ |  | |

EXAMPLE 26

Ointment

| | | |
|----|---|----|
| 5 | Compound of formula (I), e.g. chloromethyl 17 α -ethoxycarbonyloxy-11 β -hydroxyandrost-4-en-3-one-17 β -carboxylate or chloromethyl 11 β -hydroxy- | 5 |
| 10 | 17 α -isopropoxycarbonyl-oxyandrost-4-en-3-one-17 β -carboxylate Liquid paraffin White soft paraffin | 10 |
| 15 | 0.2% w/w 10.0% w/w 89.8% w/w | 15 |

Aphthous Ulcer Pellet

| | | |
|----|---|----|
| 20 | Compound of formula (I), as above Lactose Acacia Magnesium stearate | 20 |
| | 0.25 mg 69.90 mg 3.00 mg 0.75 mg | |

Retention Enema

| | | |
|----|--|----|
| 25 | Compound of formula (I), as above Tween 80 Ethanol Propylparaben Methylparaben Distilled water | 25 |
| | 0.001% w/v 0.05% w/v 0.015% w/v 0.02% w/v 0.08% w/v q.s. 100 volumes | |

Eye Drops

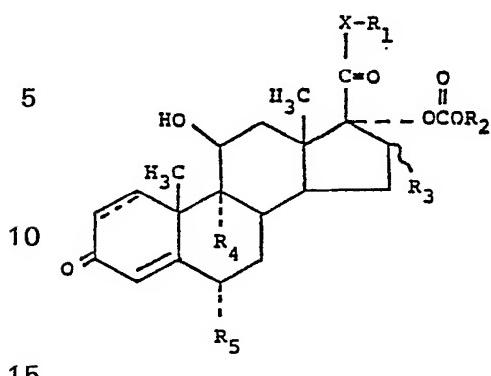
| | | |
|----|--|----|
| 35 | Compound of formula (I), as above Tween 80 Ethanol Benzalkonium chloride Phenyl ethanol Sodium chloride Water for injection | 35 |
| | 0.1% w/v 2.5% w/v 0.75% w/v 0.02% w/v 0.25% w/v 0.60% w/v q.s. 100 volumes | |

EXAMPLE 27

Ointment

| | | |
|----|--|----|
| 45 | Compound of formula (I), e.g. chloromethyl 17 α -ethoxycarbonyloxy-9 α -fluoro-11 β -hydroxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate or chloromethyl 9 α -fluoro-11 β -hydroxy-17 α -methoxycarbonyloxy-16 α -methylandrosta-1,4-dien-3-one-17 β -carboxylate Liquid paraffin White soft paraffin | 45 |
| 50 | 0.025% w/w 10.175% w/w 89.8% w/w | 50 |
| 55 | | 55 |

| | | |
|----|--|------------------|
| | <i>Aphthous Ulcer Pellet</i> | |
| | Compound of formula (I), e.g. chloromethyl 9 α -fluoro- | |
| | 11 β -hydroxy-17 α - | |
| 5 | isopropoxycarbonyloxy-16 β - methylandrosta-1,4-dien-3- one-17 β -carboxylate or chloromethyl 17 α - | 5 |
| 10 | ethoxycarbonyloxy-9 α -fluoro- 11 β -hydroxy-16 α - methylandrosta-1,4-dien-3- one-17 β -carboxylate | 10 |
| | Lactose | 0.1 mg |
| | Acacia | 69.90 mg |
| 15 | Magnesium stearate | 3.0 mg |
| | | 0.75 mg |
| | | 15 |
| | <i>Retention Enema</i> | |
| | Compound of formula (I), e.g. chloromethyl 11 β - | |
| 20 | hydroxy-17 α - isopropoxycarbonyloxy- androsta-1,4-dien-3-one- 17 β -carboxylate or chloromethyl 9 α -fluoro- | 20 |
| 25 | 11 β -hydroxy-17 α - isopropoxycarbonyloxy- 16 β -methylandrosta-1,4- dien-3-one-17 β -carboxylate | 25 |
| | Tween 80 | 0.001% w/v |
| 30 | Ethanol | 0.05% w/v |
| | Propylparaben | 0.015% w/v |
| | Methylparaben | 0.02% w/v |
| | Distilled water | 0.08% w/v |
| | | q.s. 100 volumes |
| 35 | <i>Eye Drops</i> | 35 |
| | Compound of formula (I), e.g. chloromethyl 9 α - fluoro-11 β -hydroxy-16 α - methyl-17 α -propoxy- | |
| 40 | carbonyloxyandrosta-1,4- dien-3-one-17 β -carboxylate | 40 |
| | or chloromethyl 9 α -fluoro- 11 β -hydroxy-17 α -methoxy- carbonyloxy-16 α -methyl- | |
| 45 | androsta-1,4-dien-3-one- 17 β -carboxylate | 45 |
| | Tween 80 | 0.025% w/v |
| | Ethanol | 2.5% w/v |
| | Benzalkonium chloride | 0.75% w/v |
| 50 | Phenyl ethanol | 0.02% w/v |
| | Sodium chloride | 0.25% w/v |
| | Water for injection | 0.60% w/v |
| | | q.s. 100 volumes |
| 55 | From the foregoing description, one of ordinary skill in the art can readily ascertain the essential characteristics of the present invention and, without departing from the spirit and scope thereof, can make various changes in and/or modifications of the invention to adapt it to various usages and conditions. As such, these changes and/or modifications are properly, equitably and intended to be within the full range of equivalence of the following claims. | 55 |
| 60 | CLAIMS | 60 |
| | 1. A compound selected from the group consisting of: | |
| | (a) a compound of the formula | |



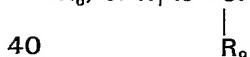
wherein:

- 20 R₁ is C₁-C₁₀ alkyl; C₂-C₁₀ (monohydroxy or polyhydroxy)alkyl; C₁-C₁₀ (monohalo or polyhalo)-alkyl; or -CH₂COOR₆ wherein R₆ is unsubstituted or substituted C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl or C₂-C₁₀ alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl.



unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxy carbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl; or R_1 is $-\text{CH}_2\text{CONR}_7\text{R}_8$ wherein R_7 and R_8 , which can be the same or different, are each hydrogen, lower alkyl, C_3-C_8 cycloalkyl, phenyl or benzyl, or R_7 and R_8 are combined such that $-\text{NR}_7\text{R}_8$ represents the residue of a saturated monocyclic secondary amine; or R_1 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group of phenyl and benzyl substituents defined hereinabove with respect to

R₆; or R₁ is -CH-Y- (lower alkyl) wherein Y is -S-, -SO-,



$\text{--SO}_2\text{--}$ or --O-- and R_9 is hydrogen, lower alkyl or phenyl, or R_9 and the lower alkyl group adjacent to Y are combined

- 45 so that R₁ is a cyclic system of the type -CH— Y
 | |
 alkylene

wherein Y is defined as above and the alkylene group contains 3 to 10 carbon atoms, of which
50 at least 3 and

no more than 6 are ring atoms; or R_1 is $-\text{CH}-\text{OCR}_6$ wherein
55 R_{10}

R₆ is defined as hereinabove and R₁₀ is hydrogen, lower alkyl, phenyl or halophenyl;
 R₂ is unsubstituted or substituted C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkenyl or C₂-C₁₀
 60 alkenyl, the substituents being selected from the group consisting of halo, lower alkoxy, lower alkylthio, lower 60

5 alkylsulfinyl, lower alkylsulfonyl, $-\text{NHC}-$ ($\text{C}_1\text{--C}_{10}$ alkyl) 5

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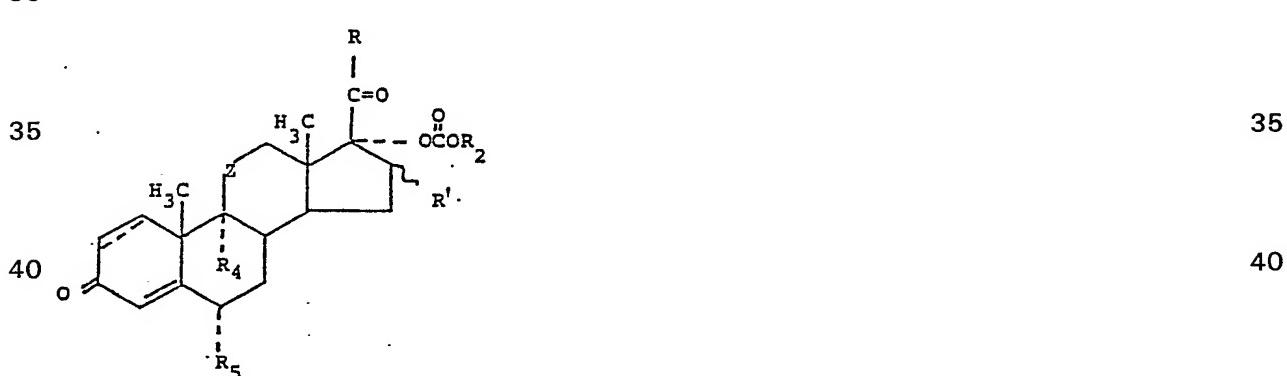
and $-\text{OC}(=\text{O})-$ ($\text{C}_1\text{--C}_{10}$ alkyl), or R_2 is unsubstituted or substituted phenyl or benzyl, the substituents being selected from the group consisting of lower alkyl, lower alkoxy, halo, carbamoyl, lower alkoxy carbonyl, lower alkanoyloxy, lower haloalkyl, mono(lower alkyl)amino, di(lower alkyl)amino, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl, lower alkylthio, lower alkylsulfinyl and lower alkylsulfonyl;

15 15

R_3 is hydrogen, α -hydroxy, β -hydroxy, α -methyl

O
||

β -methyl, $=\text{CH}_2$, or α - or β - OCOR_2 wherein R_2 is identical
 20 to R_2 as defined hereinabove;
 R_4 is hydrogen, fluoro or chloro;
 R_5 is hydrogen, fluoro, chloro or methyl;
 X is $-\text{O}-$ or $-\text{S}-$;
 25 Z is carbonyl or β -hydroxymethylene;
 and the dotted line in ring A indicates that the 1,2 linkage is saturated or unsaturated;
 and a quaternary ammonium salt of the compound represented by said formula wherein at
 least one of R_1 and R_2 is a halo-substituted alkyl group; and
 (b) a compound of the formula
 25



wherein:

wherein:
 R_2 , R_4 , R_5 , Z and the dotted line in ring A are as defined above;
 R is hydroxy; chloro; OM wherein M is alkali metal, alkaline earth metal/2, thallium or NH_4 ;
50 or OR₁ wherein R₁ is as defined above;
 R' is R₂'' or R₂'''', R₂''' being hydrogen, α -methyl.

O

Y is $-S-$, $-SO-$, $-SO_2-$ or $-O-$; or $-CH_2-OCR_6''$ wherein R_6''

5

is C_1-C_6 alkyl or phenyl; R_2 is C_1-C_6 alkyl; C_3-C_8 cycloalkyl; phenyl; benzyl or C_1-C_6 (monohalo or polyhalo)-alkyl; R_3 is hydrogen; α -hydroxy; α -methyl; β -methyl or

5

O

$\alpha-OCOR_2$ wherein R_2 is as defined above; R_4 is hydrogen or

10

fluoro; and R_5 is hydrogen or fluoro.

4. A compound of claim 3 wherein Z is β -hydroxymethylene.

10

15 5. A compound of claim 4 wherein R_1 is C_1-C_6 (monohalo or polyhalo)alkyl.

15

6. A compound of claim 5 wherein R_2 is C_1-C_6 alkyl.

7. A compound of claim 5 wherein R_2 is C_3-C_8 cycloalkyl, phenyl, benzyl or C_1-C_6 (monohalo or polyhalo)-alkyl.

8. A compound of claim 6 or 7 wherein X is $-O-$.

20

20 9. A compound of claim 8 wherein R_4 and R_5 are hydrogen.

10. A compound of claim 8 wherein R_4 is fluoro and R_5 is hydrogen.

11. A compound of claim 10 wherein R_3 is α -methyl or β -methyl.

12. A compound of claim 3 wherein Z is carbonyl.

13. A compound of claim 4, said compound being selected from the group consisting of

25

25 chloromethyl 11β -hydroxy- 17α -methoxycarbonyloxyandrost-4-en-3-one- 17β -carboxylate, chloromethyl 17α -ethoxycarbonyloxy- 11β -hydroxyandrost-4-en-3-one- 17β -carboxylate, chloromethyl 17α -butoxycarbonyloxy- 11β -hydroxyandrost-4-en-3-one- 17β -carboxylate, chloromethyl 11β -hydroxy- 17α -isopropoxycarbonyloxyandrost-4-en-3-one- 17β -carboxylate, 1-chloroethyl 11β -hydroxy- 17α -isopropoxycarbonyloxyandrost-4-en-3-one- 17β -carboxylate, chloromethyl 17α -ethoxy-
30 carbonyloxy- 11β -hydroxyandrosta-1,4-dien-3-one- 17β -carboxylate and chloromethyl 11β -hydroxy- 17α -isopropoxycarbonyloxyandrosta-1,4-dien-3-one- 17β -carboxylate.

30

14. A compound of claim 4, said compound being selected from the group consisting of chloromethyl 17α -ethoxycarbonyloxy- 9α -fluoro- 11β -hydroxy- 16β -methylandrosta-1,4-dien-3-one- 17β -carboxylate, chloromethyl 9α -fluoro- 11β -hydroxy- 16α -methyl- 17α -propoxycarbonyloxyan-

35

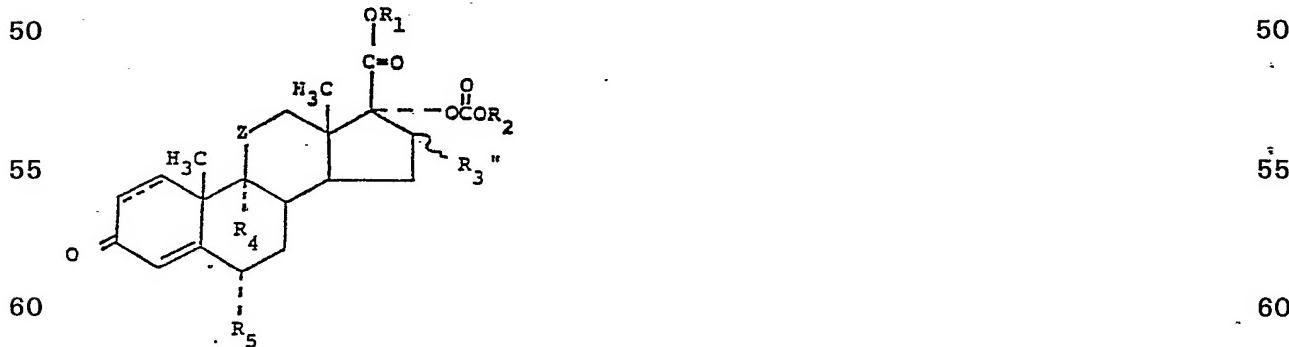
35 drosta-1,4-dien-3-one- 17β -carboxylate, 1-chloroethyl 9α -fluoro- 11β -hydroxy- 17α -isopropoxycarbonyloxy- 16β -methylandrosta-1,4-dien-3-one- 17β -carboxylate, chloromethyl 17α -ethoxy-carbo-
nyloxy- 9α -fluoro- 11β -hydroxyandrosta-1,4-dien-3-one- 17β -carboxylate, chloromethyl 17α -ethoxycarbonyloxy- 9α -fluoro- 11β -hydroxy- 16α -methylandrosta-1,4-dien-3-one- 17β -carboxylate,
chloromethyl 9α -fluoro- 11β -hydroxy- 17α -isopropoxycarbonyloxy- 16α -methylandrosta-1,4-dien-3-

35

40 one- 17β -carboxylate, chloromethyl 9α -fluoro- 11β -hydroxy- 17α -isopropoxycarbonyloxy- 16β -me-
thylandrosta-1,4-dien-3-one- 17β -carboxylate, chloromethyl 9α -fluoro- 11β -hydroxy- 17α -methoxy-
carbonyloxy- 16α -methylandrosta-1,4-dien-3-one- 17β -carboxylate, chloromethyl 9α -fluoro- 11β -
hydroxy- 16α -methyl- 17α -pentyloxycarbonyloxyandrosta-1,4-dien-3-one- 17β -carboxylate, fluoromethyl
45 17α -ethoxycarbonyloxy- 9α -fluoro- 11β -hydroxy- 16α -methylandrosta-1,4-dien-3-one- 17β -
carboxylate and methyl 17α -(2-chloroethoxy)carbonyloxy- 9α -fluoro- 11β -hydroxy- 16α -methylandrosta-1,4-dien-3-one- 17β -carboxylate.

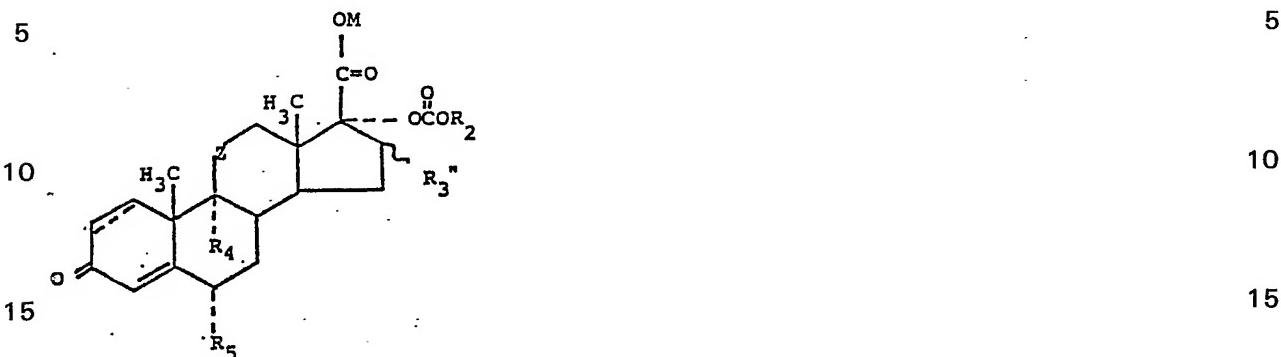
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45 15. A process for preparing a compound represented by the formula:



65 65 wherein R_1 , R_2 , R_3'' , R_4 , R_5 , Z and the dotted line in ring A are as defined in claim 1, (a), with 65

the proviso that R₁ and R₂ is not a sulfinyl- or sulfonyl- containing group, and a quaternary ammonium salt thereof, comprising reacting a compound represented by the formula

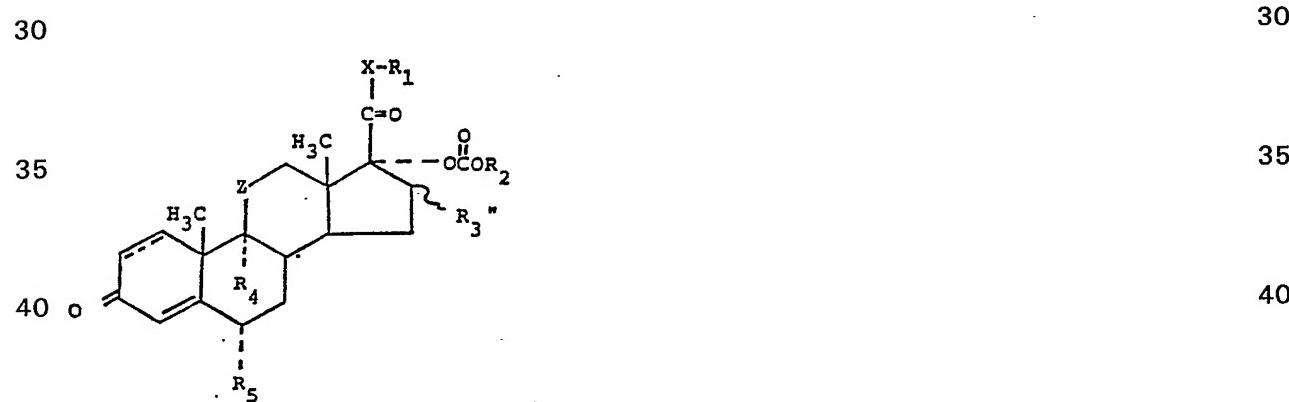


wherein R₂, R_{3''}, R₄, R₅, Z and the dotted line in ring A are defined as above, and M is alkali metal, alkaline earth metal/2, tellium or NH₄ with a compound represented by the formula

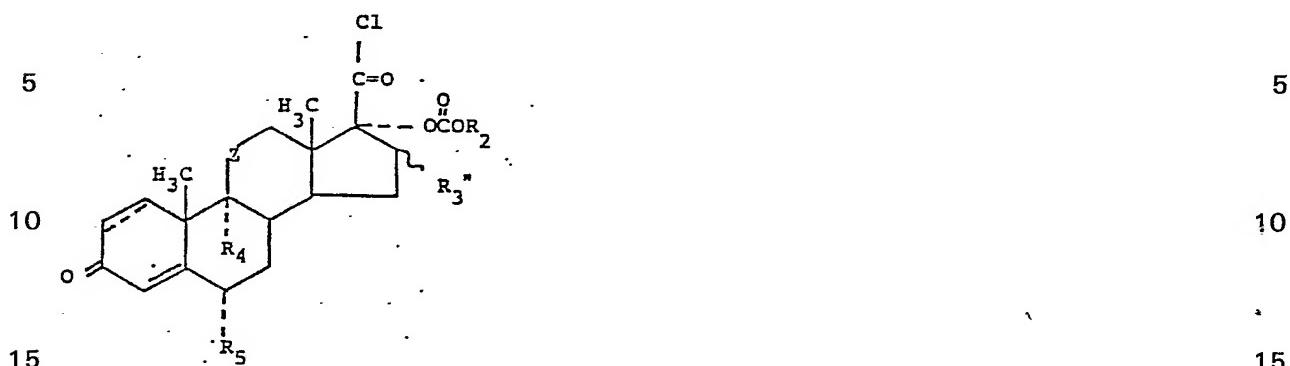
R₁W

25 wherein R₁ is defined as above, and W is halogen, and, if desired, reacting the compound obtained above wherein at least one of R₁ and R₂ is a halo-substituted alkyl group with a tertiary amine or an unsaturated amine.

16. A process for preparing a compound represented by the formula:



wherein R₁, R₂, R_{3''}, R₄, R₅, Z and the dotted line in ring A are as defined in claim 15, and X is -O- or -S-, and a quaternary ammonium salt thereof, the process comprising reacting a compound represented by the formula

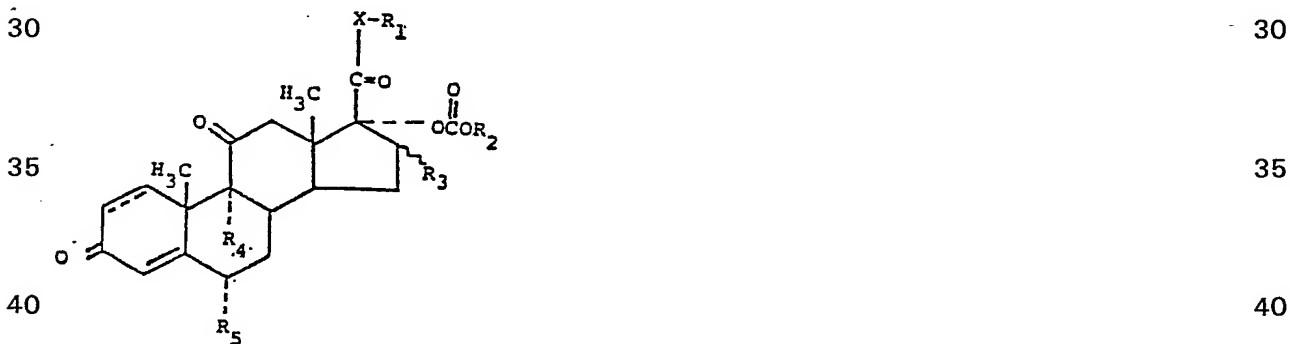


wherein R_2 , R_3'' , R_4 , R_5 , Z and the dotted line in ring A are defined as above, with a compound
20 represented by the formula

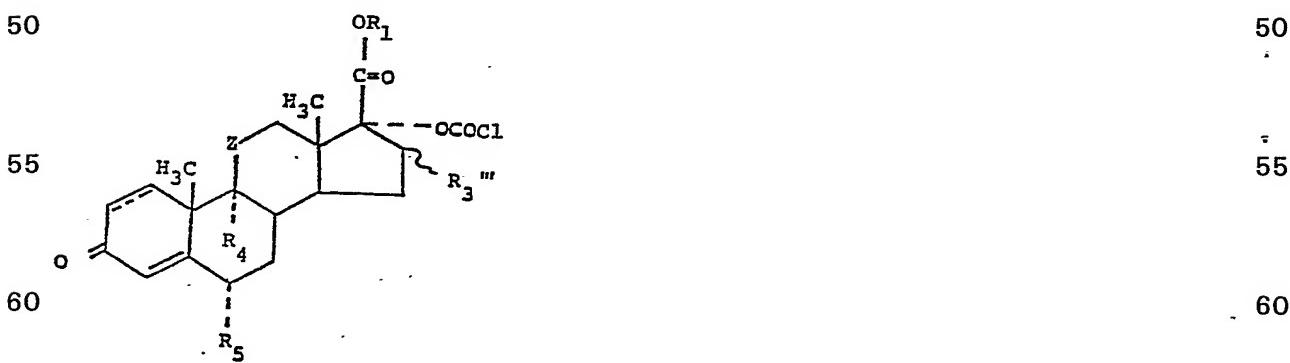
R₁XM'

wherein R₁ and X are as defined above, and M' is hydrogen or M wherein M is as defined in
25 claim 1, (a), and, if desired, reacting the compound obtained above wherein at least one of R₁
and R₂ is a halo-substituted alkyl group with a tertiary amine or an unsaturated amine. 25

17. A process for preparing a compound represented by the formula:



45 wherein R₁, R₂, R₄, R₅, Z and the dotted line in ring A are as defined in claim 15, and X and R' are as defined in claim 1, (a), and a quaternary ammonium salt thereof, the process comprising reacting a compound represented by the formula



wherein R₁, R₄, R₅, Z and the dotted line in ring A are defined as above, and R_{3'''} is as defined in claim 1 with a compound represented by the formula

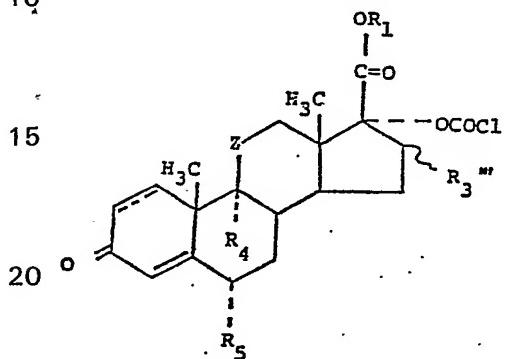
5 R₂OM'

wherein R₂ is as defined above, and M' is as defined in claim 16, and, if desired, reacting the compound obtained above wherein at least one of R₁ and R₂ is a halo-substituted alkyl group with a tertiary amine or an unsaturated amine.

18. A process for preparing a compound represented by the formula:

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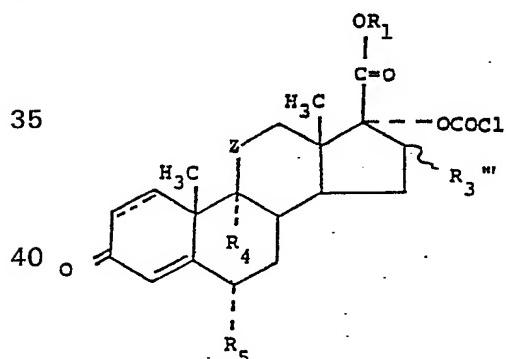
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25

wherein R₁, R₂, R₄, R₅, Z and the dotted line in ring A are as defined in claim 15, and R₃ is as defined in claim 1, (a), and a quaternary ammonium salt thereof, the process comprising reacting a compound represented by the formula

30

30



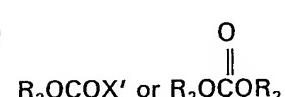
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45

wherein R₁, R₄, R₅, Z and the dotted line in ring A are defined as above, and R_{3'} is hydrogen, α-methyl, β-methyl, =CH₂, α-OH or β-OH with a compound represented by the formula

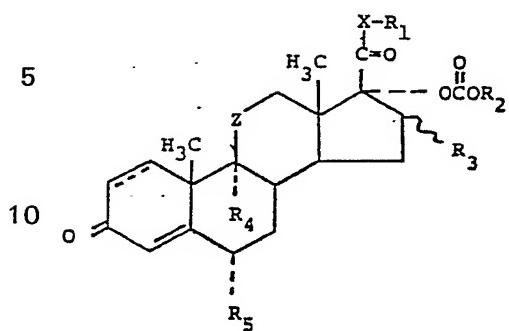
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50



wherein R₂ is as defined above, X' is chloro or bromo, and, if desired, reacting the compound obtained above wherein at least one of R₁ and R₂ is a halo-substituted alkyl group with a tertiary amine or an unsaturated amine.

19. A process for a preparing a compound represented by the formula



5

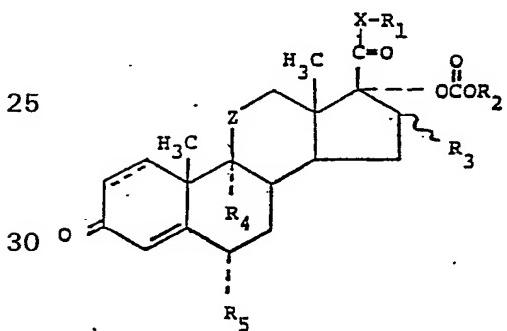
10

15

wherein R₁, R₂, R₃, R₄, R₅, X, Z and the dotted line in ring A are as defined in claim 1, (a), with the proviso that at least one of R₁ and R₂ is a sulfinyl- or sulfonyl-containing group, the process comprising the step of oxidizing a compound represented by the formula

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20



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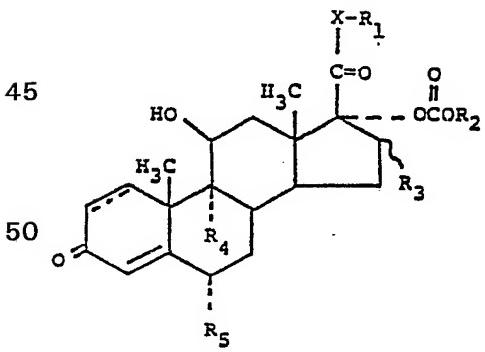
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35

wherein R₃, R₄, R₅, X, Z and the dotted line in ring A are as defined above, and R₁ and R₂ are as defined in claim 1, (a), with the proviso that at least one of R₁ and R₂ is a sulfur-containing group.

20. A process for preparing a compound represented by the formula

40

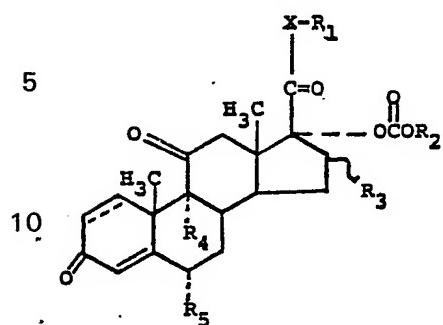


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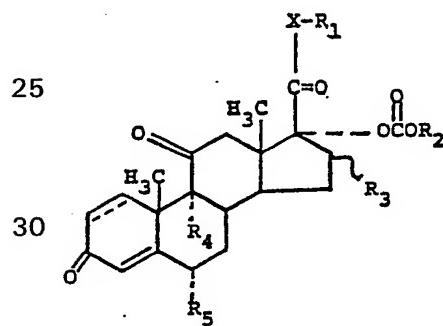
55

wherein R₁, R₂, R₃, R₄, R₅, X and the dotted line in ring A are as defined in claim 1, (a), and a quaternary ammonium salt thereof, the process comprising reducing a compound represented by the formula

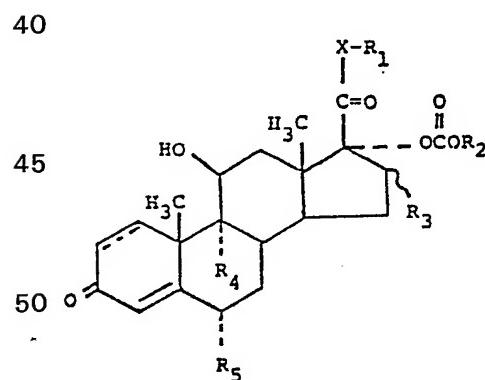


wherein R_1 , R_2 , R_3 , R_4 , R_5 , X and the dotted line in ring A are as defined above, and, if desired, reacting the compound obtained above wherein at least one of R_1 and R_2 is a halo-substituted alkyl group with a tertiary amine or an unsaturated amine.

20 21. A process for preparing a compound represented by the formula

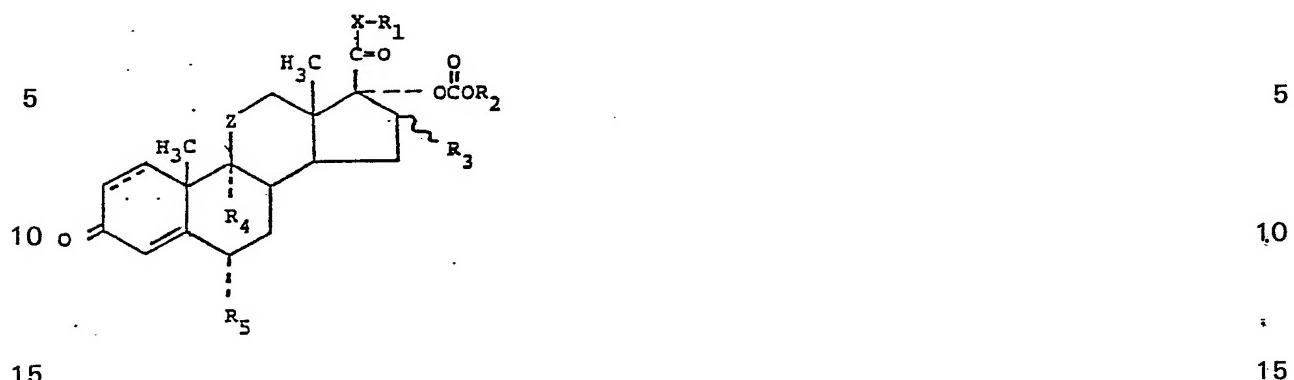


wherein R_1 , R_2 , R_3 , R_4 , R_5 , X and the dotted line in ring A are as defined in claim 1, (a), the process comprising the step of oxidizing a compound represented by the formula



55 wherein R_1 , R_2 , R_3 , R_4 , R_5 , X and the dotted line in ring A are as defined above.

22. A pharmaceutical composition of matter comprising an anti-inflammatory effective amount of a compound represented by the formula



wherein R₁, R₂, R₃, R₄, R₅, X, Z and the dotted line in ring A are as defined in claim 1, (a), in combination with a non-toxic pharmaceutically acceptable carrier therefor suitable for topical or other local application.

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